

Innate Immunity in Atopic Dermatitis

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Abstract Atopic dermatitis (AD) is a clinically defined, highly pruritic, chronic inflammatory skin disease. In AD patients, the combination of a genetic predisposition for skin barrier dysfunction and dysfunctional innate and adaptive immune responses leads to a higher frequency of bacterial and viral skin infections. The innate immune system quickly mobilizes an unspecific, standardized first-line defense against different pathogens. Defects in this system lead to barrier dysfunction which results in increased protein allergen penetration through the epidermis and predisposes to secondary skin infections. Two loss-of-function mutations in the epidermal filaggrin gene are associated with AD. Also, inducible endogenous antibiotics such as the antimicrobial peptides cathelicidin and the beta-defensins may show defective function in lesional AD skin. Eczema herpeticum is a disseminated viral infection almost exclusively diagnosed in AD patients, which is based on unmasking of the viral entry receptor nectin-1, lack of cathelicidin production by keratinocytes, and depletion of Type I IFN-producing plasmacytoid dendritic cells from AD skin. Future therapeutic approaches to AD may include enhancement of impaired innate in addition to down-regulation of dysfunctional adaptive immunity.

Keywords Innate immunity · Atopic dermatitis · Viral skin infection · Antimicrobial peptides · Epidermal barrier dysfunction · Plasmacytoid dendritic cells

Abbreviations

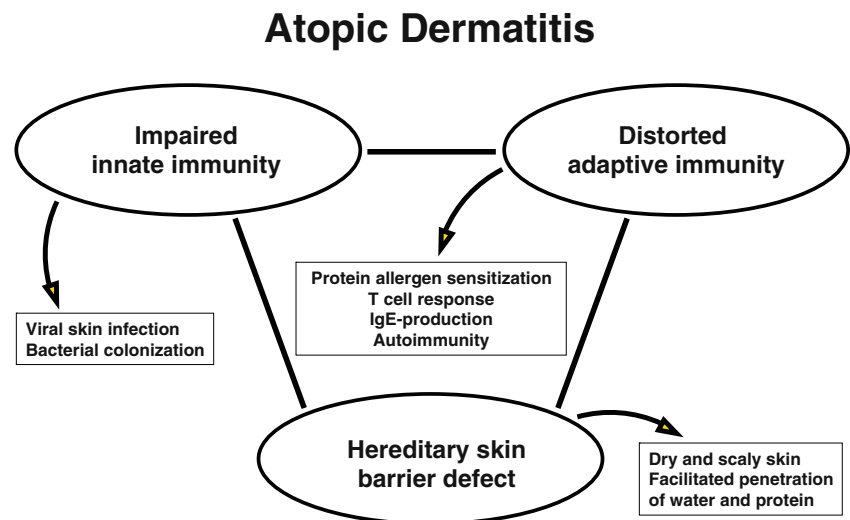
AD	Atopic dermatitis
AMP	Antimicrobial peptides
APC	Antigen-presenting cell
DC	Dendritic cell
EH	Eczema herpeticum
EM	Eczema molluscatum
Fc�RI	High-affinity IgE receptor
FPR-1	Formyl peptide receptor
HBD	Human beta-defensin
HSV	Herpes simplex virus
IDEC	Inflammatory dendritic epidermal cell
IFN	Interferon
IL18-BP	Interleukin-18 binding protein
iNOS	Inducible NO synthase
KVE	Kaposi's varicelliform eruption
LC	Langerhans cell
MCV	<i>Molluscum contagiosum</i> virus
NK	Natural killer cell
PAMP	Pathogen-associated molecular pattern
PDC	Plasmacytoid dendritic cell
PRR	Pathogen recognition receptor
<i>S. aureus</i>	<i>Staphylococcus aureus</i>
TLR	Toll-like receptor

Introduction

Atopic dermatitis (AD) is a clinically defined chronic inflammatory skin disease with a high incidence in industrialized countries. AD is characterized by a complex genetic background, a disturbed immune system, environmental trigger factors, and typical skin manifestations (Fig. 1) [1, 2]. AD patients show malfunctioning innate

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Fig. 1 Immunopathogenesis of atopic dermatitis



and adaptive immune responses and have a strong tendency to mount Th2 responses with the secretion of IL-4 and IL-13 upon exposure to environmental allergens as well as pathogens. The mechanisms of dysfunctional immune regulation in AD have been addressed in numerous clinical and experimental studies. From a functional view, the human immune system may be divided into an adaptive and an innate immune system. Whereas the latter is defined by and has the advantage of a learning capacity, the former does not learn but is quicker in its reaction (Fig. 2). It makes more sense to apply this delineation to immune mechanisms than to entire cells because most cell types play a role in both innate and adaptive immunities.

Although many clinical features of AD are direct consequences of the AD patient’s tendency to mount Th2-skewed immune responses using their acquired immune system, innate immunity is also disturbed in AD patients [3]. Secondary cutaneous infections of lesional skin with viruses, bacteria, and fungi play a major role in the clinical course of AD and cause the most severe complications of this disease [4, 5]. In this article, we will review selected

aspects and players of the cutaneous innate immune system, present clinical aspects of dysfunctional innate immunity in AD, and discuss current knowledge on the pathophysiology of infectious complications in this disease.

Delineation and Basic Aspects of Innate and Adaptive Immunity

The innate immune system comprises all inborn defense mechanisms which protect an individual by inducing immediate responses against potentially harmful microorganisms such as bacteria, fungi, and viruses. These “no-need-to-learn” mechanisms start with an intact epidermal barrier, but also include the expression and secretion of antimicrobial peptides (AMP) upon recognition of pathogens by toll-like receptors (TLR). Innate immunity includes resident cells such as keratinocytes as well as dendritic cell (DC) and lymphocyte subsets. The risk of autoimmunity in innate immune mechanisms is low but not zero [6], and goes along with the disadvantage of non-improving

Fig. 2 Key features of innate versus adaptive immunity

Key features of innate versus adaptive immunity

Innate immune system

- Inborn defense mechanisms
- No time delay
- Same reaction with repeated exposure
- Pattern recognition technique
- Inborn pathogen receptors
- Same receptors on all cells
- Low risk of autoimmunity
- Bacterial and viral components

Adaptive immune system

- Acquired defense mechanisms
- Considerable reaction time
- Improved reaction with repeated exposure
- Specific protein recognition
- Somatic recombination during life
- Different cell clones
- Considerable risk of autoimmunity
- Any protein structure

responses with repeated exposure. Some species such as frogs rely on innate immunity as their one and only defensive system.

In contrast, adaptive immunity summarizes all of the acquired but time-delayed defense mechanisms against pathogens. This part of the immune system is able to “learn”, i.e., it is able to improve its reactions with repeated exposure. In contrast to innate immune mechanisms, it requires somatic recombination which leads to different cell clones and thus is capable of specific protein recognition instead of simple pattern recognition. These immune responses may be built against virtually any structural protein. In contrast to innate immunity, adaptive immunity mechanisms possess a much higher risk of autoimmunity (Fig. 2).

It is important to understand that innate and adaptive immune mechanisms do not simply coexist but are linked to one another in a complex network of immunobiological mechanisms. Though the molecular basis of some relevant mechanisms is known, clinical knowledge suggests that many more pathways are still to be discovered.

Impaired Epidermal Barrier Function

An intact epidermal barrier may be regarded as the first and most essential component of the innate immune system. In lesional skin in AD, numerous histologically and immunobiologically well-characterized changes can be found in contrast to normal human skin, including a thick but dysfunctional epidermal layer, a pronounced lymphohistiocytic infiltrate, and a lack of inducible endogenous antibiotics [1, 7, 8]. Not only lesional but also non-lesional AD skin differs from normal human skin [9]. Non-lesional AD skin shows high transepidermal water loss, low sebum secretion, and minimal signs of an inflammatory infiltrate [10, 11]. This results in increased penetration of protein allergens or other bioactive substances such as pollen-associated lipid mediators through the impaired epidermal barrier [12]. As a consequence, allergic sensitization to a multitude of possible allergens is frequent among AD patients. This can be tested by the atopy patch test technique, which is standardized by the European Task Force on Atopic Dermatitis, and a highly specific procedure. This test relies on intact protein allergen penetration through clinically uninvolved skin without prior destruction of the epidermal barrier by tape stripping or other procedures [13].

A few years ago, key aspects of the molecular basis of epidermal barrier dysfunction were elucidated. Two loss-of-function mutations of the filaggrin gene were found to cause ichthyosis vulgaris [14]. Filaggrin is a filament-aggregating protein important in the formation of an intact stratum corneum. The two loss-of-function mutations, as well as another rare mutation in the filaggrin gene, were

found to be strong predisposing factors for AD [15–17]. The fact that more than one third of all ichthyosis vulgaris patients suffer from AD and about 2–4% of all AD patients are diagnosed with ichthyosis vulgaris at the same time [18] implicated a connection between both diseases.

Environmental exposure to allergens, proteases, soaps, and detergents may further impair epidermal barrier function [8]. The IL-4- and IL-13-dominated inflammatory cytokine milieu in atopic skin further reduces filaggrin production in AD lesions, thus, contributing to epidermal barrier dysfunction in AD [19]. These findings indicate that epidermal barrier defects may have a leading role and is probably a primary event in AD, also predisposing to secondary infections of the skin [5]. This is mirrored by the well-established clinical relevance of daily emollient application to non-lesional skin of AD patients [20].

Pathogen-Associated Molecular Patterns and Pathogen Recognition Receptors

In innate immunity, pathogen-associated molecular patterns (PAMP), such as specific motifs of bacterial or viral DNA, RNA, or proteins, are recognized through a pattern recognition system provided by a limited number of inborn pathogen recognition receptors (PRR) [21]. These pathogen recognition receptors comprise 12 members of the Toll-like receptor (TLR) family which have been identified in mammals [22]. Moreover, the mannose receptor (CD206), formyl peptide receptor (FPR1), and complement receptors may also be regarded as pathogen receptors of innate immune system [23, 24]. Patterns recognized by the innate immune system involve double-stranded viral RNA (TLR-3), single-stranded viral RNA (TLR-7), CpG motifs from bacterial DNA (TLR-9), LPS from gram-negative bacterial membranes (TLR-4), FMLP from bacterial proteins (FPR-1), mannose-rich glycans from microbial glycoproteins and glycolipids (CD206), bacterial lipoteichoic acid (TLR-2), and flagellin from bacterial flagella (TLR 5) [25]. Therapeutic activation of selected TLR pathways may be achieved by small molecules such as imiquimod or by specific CpG motifs in bacterial-like DNA fragments to modulate or initiate specifically desired immune responses [26, 27]. Binding of PAMPs to PRRs leads to activation of intracellular signaling cascades such as the NfκB pathway and secretion of innate effector molecules such as cytokines or antimicrobial peptides.

Antimicrobial Peptides

Antimicrobial peptides (AMP) function as endogenous antibiotics and play an important part in cutaneous innate

immunity [28]. The production of AMP is a mechanism used by many species for fighting invading microorganisms such as bacteria, fungi, and viruses or immediate defense after damage of the epithelial surface [29]. A single cathelicidin AMP and a number of defensin AMPs have been characterized in man [30]. Whereas the human beta-defensin (HBD)-1 is constitutively expressed by normal human keratinocytes, skin inflammation induces the expression of HBD-2, HBD-3, and the cathelicidin peptide LL-37. The expression of inducible AMP in AD lesions was significantly reduced if compared to psoriasis [7]. Therefore, it has been suggested that a lack of AMP contributes to the increased susceptibility of AD patients for disseminated viral skin infections, which is not the case for psoriasis patients [31, 32]. However, this view has been challenged by several groups in the meantime, as an increased expression and secretion of AMP, and especially cathelicidin, has been demonstrated in AD lesions and superficial skin injury in AD [33, 34]. Dysfunctional induction of cathelicidin has been demonstrated in injured lesional skin in AD in another study, which could contribute to the increased susceptibility of AD patients to skin infections [35]. Clinical and experimental data support the view that AD patients with a history of eczema herpeticum show a defective upregulation of AMP [32, 36].

The cutaneous regulation of AMP expression has been extensively studied during the last years. While defensin expression is controlled by proinflammatory mediators such as $\text{TNF}\alpha$, the factors controlling cathelicidin expression remained unknown for a long time. Unexpectedly, vitamin D3 was identified as the sole factor inducing cathelicidin in keratinocytes, and in the meantime, critical elements involved in cathelicidin control in the skin have been identified [29, 37–40]. These observations stimulated experimental and clinical trials, which investigated whether improved vitamin D3 metabolism would affect cutaneous innate immunity. Indeed, keratinocytes produce and activate vitamin D3 under the influence of UVB irradiation in sufficient concentration to activate cathelicidin expression in an autocrine fashion [41]. Narrow-band UVB irradiation increases vitamin D3 and cathelicidin levels in the skin of AD patients [42]. Oral supplementation of vitamin D3 increases cathelicidin expression in AD lesions [43]. Further studies are needed to establish a firm link between AMP expression and infectious complications in AD patients and the use of vitamin D3 to prevent these [29].

Dendritic Cell Subsets in AD Lesions

Dendritic cells (DCs) are a morphologically and functionally defined family of antigen-presenting cells (APCs) which are found in small percentages in most organs of the human body.

DCs initiate primary and secondary adaptive immune responses. Cell lineage, localization, and immunophenotype determine nomenclature of DC [2, 44]. Skin dendritic cells are subdivided after their immunophenotype into normal Langerhans cells, inflammatory dendritic epidermal cells, and plasmacytoid dendritic cells (PDCs) [45]. Langerhans cells (LCs) are DCs of the normal epidermis and defined as bone marrow-derived, epidermally located, dendritic APCs that contain Birbeck granules and express CD1a and MHC class II molecules [46]. Topical glucocorticoid therapy as well as UV light exposure may deplete LCs from the epidermis. Inflammatory dendritic epidermal cells (IDECs) are defined as epidermally located dendritic cells that do not contain Birbeck granules but express CD1a, CD11b, and class II molecules [47]. These IDECs have been demonstrated in AD, psoriasis vulgaris, allergic contact eczema, mycosis fungoides, lichen planus, Dorfman–Chanarin syndrome, Netherton syndrome, Sulzberger–Garbe disease [48–50]. As the cytokines granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-4/IL-13 are abundant in AD lesions [51–54], it can be assumed that peripheral blood monocytic cells differentiate into IDECs whilst migrating into the AD lesions. IDECs express more costimulatory molecules CD80 and CD86 than LC, supporting the role of IDECs in the presentation of antigens in AD skin. [55]. The mannose receptor CD206 is also expressed on IDECs and is functional in terms of antigen uptake of mannose antigens by means of mannose receptor-mediated endocytosis [56]. Immature dendritic cells with a higher expression of high-affinity IgE receptor ($\text{Fc}\epsilon\text{RI}$), thereby resembling the IDEC phenotype, can be generated in vitro under reducing cell culture conditions [57]. Treatment of AD with the topical calcineurin inhibitor tacrolimus selectively depletes IDECs from the epidermis, reduces the $\text{Fc}\epsilon\text{RI}$ expression and the stimulatory capacity of LCs and IDECs [58]. This selective IDEC depletion phenomenon can also be induced by the topical calcineurin inhibitor pimecrolimus [59]. Topical hydrocortisone treatment increases the rate of early apoptotic DCs in situ, whereas topical tacrolimus does not [60]. Both agents decrease the expression of the costimulatory molecules CD80 and CD86 on epidermal DCs [60].

Plasmacytoid Dendritic Cells

Plasmacytoid dendritic cells (PDCs), a dendritic cell subset first described in the blood (CD123⁺⁺⁺, BDCA-2⁺, HLA-DR⁺⁺⁺), comprise 0.1% of peripheral blood mononuclear cells [61]. As PDCs produce large amounts of type I interferon ($\text{IFN-}\alpha$ and $\text{IFN-}\beta$) upon viral infection [62], they are effector cells of innate immunity. However, PDCs exhibit an intrinsic activity to induce Th2 responses [63] and regulatory T cells [64], and therefore also play a role in

adaptive immunity. Skin PDCs have been demonstrated in cutaneous lupus erythematosus [65], in psoriasis [45], and in contact dermatitis [45] in relatively high numbers, while in AD lesions, only few PDCs can be detected [45]. While the number of peripheral blood PDCs is increased in AD [66], the lack of PDCs in AD lesions seems to contribute to the high susceptibility of AD patients to viral skin infections such as eczema herpeticum [4]. Crosslinking of FcεRI on PDCs reduces type I interferon production induced by TLR-9 induction [67] and the stimulatory capacity of PDCs [68]. Immunostimulatory CpG oligonucleotides and imiquimod work by direct stimulation of PRR expressed on PDCs [3].

Natural Killer Cells

Natural killer cells (NK cells) account for 10–15% of all peripheral blood lymphocytes. These important effector cells of the innate immune system may lyse microbial-infected or malignant target cells without prior activation. The lack of MHC-I expression is picked up by NK cells as a “missing self” signal and starts a cascade of cell lysis [69]. Target cell lysis is mediated by release of cytoplasmic granules containing the membrane-attacking perforin and the protease granzyme. NK cells produce a variety of cytokines such as IFN-γ, TNF-α, GM-CSF, IL-5, and IL-8 [70]. The number of circulating NK cells is reduced in AD [70, 71], whereas in AD lesions, NK cells have been detected in close contact to DCs [72]. Coculture of *Malassezia* antigen-stimulated DCs with NK cells may increase DC numbers in vitro [73], whereas cell-contact-dependent preferential apoptosis of NK cells by activated monocytes has also been described in AD patients [71]. This may help in deviating immune responses towards a Th2 pattern and contribute to the susceptibility to infection in AD [71].

Innate Immunity and *Staphylococcus aureus* Colonization

Colonization with *Staphylococcus aureus* is a phenomenon observed in most AD patients [1]. *S. aureus* may be cultured from skin lesions and, to a lesser extent, also from non-lesional AD skin. The nasal vestibulum is the most important reservoir for recolonization of the skin [74]. An impaired epidermal barrier, an altered innate immune system, a decreased bacterial clearance, and an increased bacterial adhesion are important pathogenic factors for staphylococcal colonization [5, 75]. The levels of the antimicrobial defensin HBD-2 and the cathelicidin LL-37, and also of IL-8 and inducible NO synthases (iNOS) were

found to be reduced in AD compared to psoriasis patients [7, 76]. Differential AMP expression in AD and psoriasis has been confirmed for HBD-2 and other antimicrobially active substances like elafin, calgranulin C, iNOS, psoriasin, and calgranulin A [77]. Although HBD-2 and LL-37 exert a synergistic antimicrobial activity, the concentration of both in AD might be too low to effectively kill *S. aureus* [7]. In extrinsic AD skin, high concentrations of IL-4 and IL-13 were shown to additionally inhibit HBD-2, IL-8, and iNOS gene expression [7, 76]. Elevated IL-10 gene expression in extrinsic and intrinsic AD was associated with a decreased HBD-2 expression [78], but here, neutralizing antibodies to IL-10 not only augmented production of HBD-2 and LL-37 but also of TNF-α and IFN-γ [78].

Another AMP with no homology to other known APM is dermcidin, which is expressed in eccrine sweat glands, secreted into sweat, and transported to the epidermis [79]. Dermcidin has a broad spectrum of activity including *S. aureus*. AD patients did not show significant reduction of bacterial skin surface colonization after sweating that was observed in healthy subjects [79] as several dermcidin-derived peptides were significantly reduced in AD compared to healthy subjects, and in AD patients with previous bacterial or viral infections, concentrations were found to be lowest [79].

Local production of staphylococcal exotoxins with superantigenic properties is the consequence of staphylococcal colonization permitted by a weak innate immune system impaired by Th2 signals [80]. Antigen-specific immune response to aero- and food allergens involving IgE-mediated, facilitated antigen presentation colocalize with polyclonal activation of T cells driven by superantigenic properties of staphylococcal exotoxins [3], which may also be a target for IgE responses in AD patients [81].

All these findings support the idea that a deficiency in various antimicrobial peptides may cause the high rate of *S. aureus* impetiginization in AD. Reduction of *S. aureus* colonization is a well-accepted therapeutic strategy for long-term management of AD, and may be achieved by the addition of antibacterial substances to the daily used emollients recommended since many years [20, 82]. In severe cases of impetiginized AD, oral antibiotic therapy with cephalosporins or penicillins is a useful strategy [82].

Eczema Herpeticum

Patients with compromised cell-mediated immunity, as present in AD, may develop recurrent and severe herpes simplex virus (HSV) infections, which may be caused by either primary or secondary HSV infection [4]. Eczema herpeticum (EH) is defined as the disseminated cutaneous

infection of an eczematous skin disease with HSV, which in clinical reality is almost exclusively AD, whereas Kaposi's varicelliform eruption is the disseminated cutaneous infection of any skin disease (not only AD, but also Darier disease, pemphigus foliaceus, mycosis fungoides, Sézary syndrome, ichthyosis vulgaris, Hailey–Hailey disease, and burns) with HSV or related viruses [83]. EH may be diagnosed based on clinical criteria by disseminated, distinctly monomorphic dome-shaped vesicles, frequently accompanied by fever, malaise, and lymphadenopathy [84]. Head and neck are most commonly affected. Associated complications include not only keratoconjunctivitis but also viremia, leading to multiple organ involvement with meningitis and encephalitis if not treated adequately [83]. The pathogenesis of EH involves an infection of keratinocytes, followed by an antiviral immune response, which must be mounted in a Th2-skewed environment. This underlying predisposition to Th2-type responses may favor HSV overgrowth [85]. Regarding innate immune mechanisms, a pathogenic factor that contributes to HSV infections in AD is the spongiosis and disruption of the compact keratinocyte layer present in AD that leads to an unmasking of the desmosomal protein nectin-1, which acts as one of the relevant entry receptors for HSV [86]. The relevance of AMP dysregulation in the pathogenesis of EH is well established [32]: Physiological concentrations of the cathelicidin LL-37 show antiviral activity against HSV in vitro, but there may be disturbed upregulation of LL-37 in AD lesions in vivo [32, 35]. Interestingly, cathelicidin peptide LL-37 expression is also inversely correlated to the serum IgE level of EH patients [32].

PDCs play a key role in the cascade of antiviral innate immune responses as they produce high amounts of antiviral type I IFN- α and IFN- β upon viral infection. Although the number of peripheral blood PDC is increased in AD [66], in skin lesions of AD, very few PDCs are found compared to other inflammatory skin diseases such as psoriasis, contact dermatitis, or lupus erythematosus [45], which can be explained by dose-dependent PDC apoptosis induction caused by IL-4, an effect that is potentiated by IL-10 [63]. Crosslinking of the high-affinity IgE receptor on PDCs reduces the type I interferon production induced by TLR-9 activation [67, 68]. So, PDC depletion and functional impairment, and therefore diminished production of antiviral type I interferons, may contribute to the predisposition of AD patients to viral skin infections [45, 67].

EH treatment should be started as soon as possible with systemic antiviral chemotherapy with nucleoside analogs such as acyclovir [4]. A 7-day course of intravenous acyclovir (5–10 mg/kg per dose i.v. t.i.d.) is currently recommended and may be prolonged according to the clinical course of the disease [4]. Oral antibiotics may be

helpful in fighting bacterial superinfection, topical antiseptics may favor the healing process by drying out vesicles and preventing infectious complications. Topical antiviral agents are usually not applied for cutaneous EH lesions as they carry a significant risk for contact sensitization and drug reactions [87], on the other hand, they offer advantages for prophylaxis and treatment of ocular complications. Lid lesions and reduced corneal sensitivity in EH should be treated prophylactically, patients with keratitis should receive combined systemic and topical therapy [4]. The administration of glucocorticosteroids in acute EH is still controversial. A number of clinicians use topical and systemic glucocorticosteroids once acyclovir has been started to favor healing of the underlying AD.

Eczema Vaccinatum

Eczema vaccinatum is defined as a disseminated eruption of *Vaccinia* lesions in AD or other pre-existing eczematous skin diseases following immunization with *Vaccinia virus* [88]. Since eczema vaccinatum is one of the few potentially life-threatening, true emergencies in clinical dermatology, vaccination is contraindicated in all patients currently affected by or having a past medical history of AD [85]. Cathelicidin AMP but not human defensins can inhibit *Vaccinia virus* growth in vitro [31]. This suggests that the eczema vaccinatum susceptibility of AD patients may be due to cathelicidin deficiency [31]. *Vaccinia virus* replicates faster in AD skin explants than in normal or psoriasis skin explants [89], and *Vaccinia virus*-induced expression of cathelicidin LL-37 peptide is reduced in AD skin [89]. This nicely demonstrates that the increased *Vaccinia* replication corresponds to a decreased expression of LL-37. The underlying cause for both observations seems to be the cytokine milieu in AD as IL-4 and IL-13 enhance *Vaccinia virus* replication and downregulate LL-37 [89, 90].

The treatment of choice for eczema vaccinatum is *Vaccinia* immune globulin, which may be combined with cidofovir and other still experimental drugs [88, 91]. Newly produced *Vaccinia* immune globulin preparations will allow an intravenous application.

Molluscum contagiosum Virus

Lesional and non-lesional skin of AD patients is susceptible to infection with *Molluscum contagiosum virus* (MCV), which is the sole member of the *Molluscipoxvirus* subfamily [4]. MCV replication in the cytoplasm is mediated by distinct enzymes which are not encoded in other DNA viruses. Umbilicated small skin-colored papules are the diagnostic hallmark of molluscum infection [18]. Patients

with AD have more frequently MCV infections than non-atopic individuals and also have more widespread disease, with up to several hundred lesions [92]. This disseminated eruption is referred to as eczema molluscum (EM) [3]. Although the first papules are frequently confined to inflamed skin regions, autoinoculation may produce papules in other areas. MCV infection does not induce clinical symptoms of systemic infection. MCV contains some genes encoding for unique host response-evasion proteins which help it avoid innate and adaptive antiviral defense mechanisms [93]. MCV produces a soluble interleukin-18 binding protein which inhibits the IL-18-mediated induction of IFN- γ [94]. This may explain the absence of T lymphocytes and NK cells at the base of typical MCV lesions [95]. Treatment of EM lesions speeds up the healing process and prevents spreading by auto- and heteroinoculation. Therefore, treatment of EM is recommended in spite of its tendency towards spontaneous regression [4]. The destruction of limited numbers of lesions with a small curved forceps or a ring curette is our treatment of choice. Other destructive treatment measures include cryotherapy or carbon dioxide laser vaporization [4]. Topical application of the TLR-7-agonist imiquimod or other topical immunostimulatory drugs is another treatment alternative [96].

Conclusion

Recent research advances allow a better understanding of the mechanisms underlying innate immune deficiency in AD patients. Several innate immune mechanisms are relevant for AD pathophysiology as these are impaired in AD patients and may contribute to the increased susceptibility of AD patients to skin infections. Also, innate and adaptive immunity do not simply coexist but are linked to one another by complex mechanisms, which are subject to current and future research. Finally, as we begin to understand the mechanisms of innate immune dysregulation in AD, the identification of possible targets for treatment or prevention will lead to novel approaches in the management of AD patients.

The pathogenesis of atopic dermatitis involves an impaired innate as well as a distorted adaptive immune response. Both mechanisms may aggravate a hereditary skin barrier defect.

Innate and adaptive immunities are different in many key features, but linked to one another through various mechanisms. Some of the signals are already known.

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