17 Allergic Contact Dermatitis and Atopic Eczema

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Patients with atopic eczema (AE) share an increased susceptibility to widespread or severe cutaneous infections. This phenomenon is considered to be due to impaired cellular immunity [1, 2]. Hence, a decreased baseline risk to become sensitized to delayed-type contact allergens (haptens) could be expected and has, indeed, been postulated by many [3–7]. Conversely, an increased risk to acquire contact allergy (CA) has been claimed by some researchers [8–11]. This controversial issue has been reviewed several times (e.g., [12–18]). On the other hand, atopic eczema modulates exposure to these very allergens, most obviously in the case of emollients and topical therapeutics used for eczema therapy. In the following chapter, we will outline and discuss clinical findings reported to date and review basic mechanism of allergic contact dermatitis (ACD) in relation to relevant pathogenetic characteristics of AE, possibly interfering with the pathogenesis of ACD.

List of Definitions

ACD Allergic contact dermatitis. A diagnosis based on history (allergen exposure correlating with course of ACD), clinical picture (exposed sites affected), and a relevant contact allergy.

AE Atopic eczema. Usually diagnosed on clinical grounds, with some variation of usage to be anticipated, notwithstanding current efforts for increased standardization [221, 222].

CA Contact allergy. Diagnosed by patch testing; clinical relevance not considered, if not stated otherwise.

PT Patch test. Occlusive application of contact allergens for 24–48 h, with test readings at least until 72 h after start of exposure. PT is still the gold standard tool to diagnose contact allergy.

17.1 Clinical Findings

17.1.1 Experimental Sensitization

The notion of decreased susceptibility to ACD in AE patients is based on several experimental studies, dating back some decades (review [14]). First sensitization experiments were done with 3-pentadecylcatechol (PDC), one of the allergenic molecules of *Rhus toxicodendron* [19]. Patients with AE, regardless of current severity, were not sensitized more often than healthy controls. However, in patients tested for a second time with the *Rhus* allergen, the frequency of active sensitization (i.e., negative in the first patch test but positive in the second) was markedly reduced (6% vs 31%) [20]. Several studies used dinitrochlorobenzene (DNCB) as experimental contact allergen in patients with AE vs controls [21–23]. In these studies with DNCB and also with PDC, a lower sensitization rate was primarily observed in patients with severe AE, defined by high total serum IgE levels: only 18% of patients with a serum IgE over 1,000 kU/l became sensitized compared with 42% with a serum IgE under 1,000 kU/l [21]. Subsequent studies using different DNCB concentrations for elicitation and including AE patients with milder symptoms, however, claimed to have found "unequivocally reduced" reactivity in theses patients, too [22]. In conclusion, experimental sensitization studies in humans do not provide a conclusive answer to the question as to whether AE patients are generally less prone to developing CA.

17.1.2 Population-Based Studies

While there are numerous epidemiological studies on AE morbidity and risk factors for AE, mostly in children and adolescents, only very few of these address the association between AE and ACD or CA:

- The Glostrup Allergy Study is possibly the only population-based study addressing the incidence of CA. None of the following were risk factors for acquisition of CA during the observation period: the "history of flexural eczema" (OR 1.06), a commonly used marker of (previous) AE, an elevated IgE level (OR 1.0), or the "at least one out of 10 prick tests positive" (OR 1.0), the latter factor being weakly related with AE [24, 25].
- In the Odense study with 12- to 16-year-old adolescents, Mortz et al. reported that "of those with ACD, 37 % had a history of AE," while in the whole study sample (n = 1,340, 1,146 of these patch tested) this proportion was 21.3 % [26].
- The KORA Allergy Study found 28 % of the general adult population (25 – 75 years) to be sensitized to at least one standard series allergen [27]; AE was not a risk factor in this older sample.

In conclusion, there is no convincing evidence of a significant association between AE and CA from population-based epidemiological studies.

17.1.3 Clinical Epidemiology

Population-based studies are often preferable over patient-based studies by virtue of unbiased estimation of morbidity and risk factor impact. However, in the field of CA they have drawbacks that impair their usefulness: (a) the positive predictive value of PT results is low due to a low prevalence of CA, i.e., a large proportion of false-positives will result; (b) for the sake of feasibility, sample size and thus power are usually limited; (c) participation rates are not in an order of magnitude that could rule out selection bias. Hence, patient-based analyses necessarily provide the bulk of evidence in the field of CA (and its association with AE).

However, due to between-center differences in the indication for patch testing AE patients, reflected by varying proportions of AE patients among patients undergoing patch testing [28], the crude prevalences of CA found in the subgroup with AE are hard to compare, both between centers and between AE and non-AE patients in one given center. In this situation, adjusted, multifactorial analyses of pooled data may offer the most valid insight into the association between AE and CA. Additionally, PT screening data obtained from whole AE populations (e.g., in an AE clinic setting) may give useful information, notwithstanding the problem of an adequate control group for comparison: a population sample is probably the best possible reference, because in patients with suspected ACD, attending a PT clinic, the prevalence of CA will be higher than normal due to this very selection [29].

17.1.4 Comparisons Between Contact Allergy Patients with or Without Atopic Eczema

A multitude of case series has been published detailing the spectrum of CA in the subset of AE patients, partly comparing CA prevalences with PT results of patients without AE [6, 7, 30, 31]. While these descriptive studies can give valuable information on the patch-reaction pattern (allergic vs doubtful reactions) [31] and the spectrum of the involved contact allergens causing CA in AE patients, their results are hardly comparable for the reasons outlined above. Furthermore, unadjusted analyses are usually heavily confounded at least by age, because (a) AE PT patients tend to be younger than patients without AE and (b) age is an important surrogate marker of a multitude of exposures to allergens, including nickel. Recently, however, an age- and sex-adjusted analysis focusing on CA to topical antibiotics and antiseptics has been published, which did not find an elevated risk of these CA in AE patients, despite presumably higher exposure [32].

Because of the presumable impact of the proportion of AE patients on the overall pattern of sensitization in a PT population – both quantitatively (increased vs decreased susceptibility to CA) and qualitatively (particular allergens in topical therapeutics) – the MOHL index [33] was extended to the MOAHL index, with "A" originally including rhinitis, asthma, or AE [34]. These indices, as well as the recent extension to the MOAHLFA index (MOAHLFA: M = Men, O = Occupational Dermatitis, A = Atopic Dermatitis, H = Hand Dermatitis, L = Leg Dermatitis, F = Face Dermatitis, A = Age > 40 years) [28], with the first "A" now denoting the proportion of patch-tested patients with previous or current AE, irrespective of mucosal symptoms, intend

to summarize important patient characteristics as background information to PT results reported.

17.1.5 Prevalence of Contact Allergy in Atopic Eczema Patients

If a group of AE patients is screened for the presence of CA, the biasing effect of selection as discussed above is not a major concern. However, selection may have a certain effect in terms of a spectrum bias, in that more severe cases of AE may be overrepresented in a clinical population of AE patients, compared with the severity spectrum on a population level. In case the common notion of "reduces susceptibility to CA" should hold true, CA prevalences should be low in such studies. However, this is not the case [35–39]. Of 73 adult patients attending a specially provided AE clinic, 42% showed one or more positive PT reactions, with a striking female preponderance [36]. Of 114 children under the age of 16 years, presenting as sequential clinic attenders with AE (42.7% mild, 47% moderate, and 10.3% severe), CA was demonstrated in 43% [38]. In this study, there was no statistically significant negative correlation between the severity of AE and CA. In a study with 251 nonselected patients with moderate or severe AE, CA was frequently found on patch testing with strong age dependency: 11% of children age 2 and below, 43% of children age 7–15, and 58% of older AE patients were diagnosed with CA [35]. The authors emphasized that the diagnosis of atopic dermatitis must not lead to focusing on IgE-dependent sensitizations without PT, because ACD may often be misdiagnosed as a flare-up of AE [13].

It was discussed that CA may be a characteristic of those AE patients who have a continuing problem with their AE [36, 40]. Therefore, the high number of patients found to be sensitized to contact allergens cannot be regarded as representative for AE patients in general, but may be a marker of a specific subgroup to be further characterized, e.g., by certain immunological features. Finally, in a prospective study in 65 patients with AE and a noneczematous control group, there was no significant difference in the occurrence of CA, except of an increased risk for sensitization to nickel [39]. The few population-based studies available found 28% of the general adult population (25–75 years) to be sensitized to at least one standard series allergen [27], or 26.4% females and 7.3% males (15- to 41-year-old Danes) [41]. Assuming that the proportion of false-positive PT results was not exceedingly high in the AE study [35], the age-stratified prevalences in AE patients thus appear high, and seem to indicate even an increased risk of CA in AE patients, or at least in a certain subpopulation of AE patients [36, 35, 13].

17.1.6 Multifactorial Analyses

The first analysis of this kind, performed by the Danish Contact Dermatitis Group, considered personal atopy, i.e., included not only AE, but also rhinitis and asthma [42]. Interestingly, despite this "dilution" of the effect of AE alone, Christophersen et al. found a decreased risk for nickel allergy, which contradicted notions of "nickel CA as minor criterion for AE" [15, 43]. In a multifactorial analysis of the North American Contact Dermatitis Group (NACDG) PT data (1985–1989), Nethercott et al. assessed the association of age, sex, site of dermatitis, coexistent irritant contact dermatitis, and AE with positive test results to standard series contact allergens [44]. With regard to AE as a risk factor for CA, only an "underrepresentation of AE in patients sensitized to p-phenylenediamine" was noted ([44], p. 15). The most current analysis, based on data collected by the Information Network of Departments of Dermatology (www.ivdk.org), found no significant association between AE as a risk factor for CA to 9 of 18 selected standard series contact allergens [45]. In seven instances (methyl[chloro]isothiazolinone, formaldehyde, fragrance mix, potassium dichromate, lanolin alcohols, thiuram mix and mercaptobenzothiazole and derivatives) a slightly increased risk for AE patients was identified, which may reflect higher exposure and/or increased false-positive test reactivity. In two allergens, a significantly lower risk for CA was found in AE patients, namely epoxy resin and nickel [46], the latter finding corroborating the results of Christophersen et al. [42].

17.1.7 Allergens

17.1.7.1 Nickel

The issue of nickel CA in patients with AE has long been the focus of dermatological and immunological research [14]. As one approach, the frequency of AE in

patients who are sensitized or not sensitized to nickel has been compared. However, without adjustment for age and sex as confounding factors, this approach is invalid. A recent adjusted analysis of clinical data, also taking into account other potential confounding factors, found no evidence of past or present AE being a risk factor for nickel CA [46]. As another approach, the frequency of nickel CA was compared between persons with AE and persons without AE (healthy controls). In the Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS), no association between nickel CA and AE was found [47]. In a study with university students from Turku, 34.0 % (25.4 %) of persons with (without) current AE had nickel CA. However, in adjusted analyses, a nonsignificantly reduced risk of nickel CA was found for atopics in this study [48] (alas, AE was not addressed).

Recently, nickel CA in relation to AE was studied not only clinically, but also immunologically [49, 50]. In view of the suppressive role of IL-10, the observation of an unchanged intralesional expression of IL-10 mRNA in AE with nickel CA, compared to increased expression after epicutaneous nickel challenge in nonatopics with nickel CA, may warrant further study; otherwise, the cytokine pattern was largely similar [49]. Recently it was shown that the in vitro proliferative (DNA synthesis) and secretory (IL-2, IL-5) response was impaired in nickel-stimulated peripheral blood mononuclear cells from patients with AE who were allergic to nickel, which might be interpreted as a hampered downregulation of ACD in AE [50].

17.1.7.2 Topical Drugs, Emulsifiers

For the treatment and prophylaxis of AE, various topical preparations are used, comprising a vast number of potential contact allergens. Hence, patients with severe and long-standing AE are heavily exposed to these allergens. Despite this, CA to various agents has not been found to be overrepresented in AE patients. For instance, while stasis dermatitis has been found to be a significant risk factor for CA to the antipruritic agent polidocanol, used (in Germany) to prevent and treat subchronic eczema, AE was not a risk factor, despite presumably similar exposure in both groups of eczema patients [51]. In a similar age- and sex-adjusted analysis, in this case excluding patients with stasis dermatitis, the prevalences of CA to a whole range of topical antibiotics and antiseptics was found to be similar in patients with or without AE. Among the allergens considered, only CA to neomycin and in particular bufexamac was (strongly) associated with AE [32]. The strong association between AE and bufexamac CA can easily be explained by the fact that this agent is predominantly used for the treatment of AE. In contrast, AE was found to be significantly, albeit weakly, associated with CA, e.g., to lanolin alcohols [45] and to the fragrance mix [52]. However, as these two (and other) contact allergens are marginal irritants under PT conditions, and patients with AE presumably are more prone to irritation, the higher proportion of irritant, false-positive PT reactions in AE patients may at least have contributed to this finding [31].

17.2 Preimmunologic Mechanisms in Allergic Contact Dermatitis

ACD is an inflammatory reaction of the skin to a xenobiotic (the allergen). Being an allergic reaction, the immune system of the skin is involved. Allergen penetration through the horny layer, into the viable epidermis, and final absorption by the lymphatic system are thus necessary prerequisites [53, 54]. Penetration of an allergen is mainly determined by two primarily independent, but interrelated factors: the molecule and the state of the skin barrier [55 – 59].

17.2.1 The Molecule

The principal factors determining the kinetics of the diffusion into the skin of a xenobiotic are the physicochemical properties of the molecule. Small, nonpolar and moderately lipophilic substances penetrate best, highly water-soluble compounds least. However, some degree of aqueous solubility is also required, since the chemical must later be diffused in the relatively aqueous viable tissue. One parameter measuring lipophilicity is the octanol/water partition coefficient (P or log P). The influence of a low lipophilicity was demonstrated in an experiment with the alkylating agent streptozotocin (STZ), composed of N-methyl-nitrosourea (the alkylating function) and a sugar moiety reducing the log P. After dermal exposure in the local lymph node assay (LLNA), STZ failed to induce a response, presum-

ably because the sugar inhibits the passage of the chemical across the stratum corneum, but after intradermal injection, STZ was able to induce proliferation of draining lymph node cells, thus confirming that the chemical is inherently allergenic, provided it can access the viable epidermis [60]. However, permeability does not necessarily correlate directly with log P because other properties such as molecular weight and the molecular size may also play a role. The threshold above which penetration should become impossible was suggested to be at 500 D [61]. Combining molecular weight and lipophilicity resulted in mathematical models to predict the penetration rate of a given molecule in terms of a quantitative structure–activity relationship [62, 63].

The "500-D rule" was recently challenged, as skin contact to proteins with weights in the range of 5,000 – 20,000 (in the case of heveins, for example [64]) was well known to cause immediate and late symptoms [56]. In food industry workers, occupational contact urticaria (protein contact dermatitis) due to several foods (e.g., meat, baking additives) is not uncommon [65]. In the atopy patch test, penetration of high-molecular-weight aeroallergens into the skin must have taken place to elicit the eczematous reaction [66]. However, the arguments in favor of the penetration of larger molecules put forward by Berard et al. [56] are based mainly on exceptional preconditions, namely the presence of an already damaged/compromised stratum corneum [65, 67]. Many individuals sensitized to natural latex are atopic [68, 69] or had pre-existing skin lesions or dermatitis [70]. Moreover, occlusion (by gloves) as well as protective creams may enhance permeation of xenobiotics [71, 72]. Dextrans (4 – 10 kD) were shown to penetrate only in conjunction with the vigorous permeation enhancer n-octyl-b- D-thioglucoside [67]. In conclusion, the general 500-D rule [61] still seems valid in most cases.

17.2.2 Skin Barrier Function

The anatomical correlate of the epidermal permeability barrier is the stratum corneum (SC), a heterogeneous, two compartment tissue, characterized as "bricks" (corneocytes consisting of bundled, water-insoluble proteins), embedded in a "mortar" of lipids, organized into characteristic lamellar structures [55, 56, 58, 59, 73 – 75]. Although the permeability of corneocytes is normally low, it was shown that several compounds (e.g., water, surfactants, low-molecular-weight moisturizers) can penetrate the corneocytes and thereby alter their water-binding capacities, which are normally controlled by the "natural moisturizing factor" (amino acids, potassium lactate, and others) [76]. Elevation of the water content (hydration) of the stratum corneum, e.g., after occlusion, causes increased permeability and physical/chemical changes. Barrier function, however, is mainly mediated by the lipid-enriched matrix, organized in stacked membrane sheets, with coexisting liquid crystalline and gel phase domains, which has been described by different models (the domain mosaic model, sandwich model, or single gel phase model) [58]. These structures are particularly suited for barrier function: diffusion of lipidic substances is more than 1,000-fold less than that found in cellular membranes. However, at least as conceived in the domain-mosaic model, water transport should not be excluded entirely, due to lacunar domains embedded within the lipid bilayers. After a permeabilizing stimulus (e.g., occlusion), they are thought to expand until they interconnect, forming a continuous pore pathway (extended macrodomain mosaic) [77]. The lipids account for approximately 20 % of the volume of the stratum corneum. This matrix is composed of roughly equimolar mixtures of ceramides (45 % – 50 % by weight), cholesterol (25 %), and long-chain fatty acids (10 % – 15 %), plus less than 5 % of several other lipids, the most important being cholesterol sulfate.

In addition to this transepidermal route, there may be a second route via appendages (pilosebaceous follicles and sweat glands). They are a potential site of discontinuity of skin barrier integrity, which are, compared to the stratum corneum, considered as zones of less resistance (shunts) to the penetration of larger molecules, such as possibly bulky proteins. Particularly the forehead and the lower leg can be regarded as such zones of lower resistance [78], which may partly explain the high sensitization risk in lower leg dermatitis [79].

17.2.3 Regulation of Epidermal Barrier Homeostasis

Although the stratum corneum has been generally viewed as an inert structure, modern concepts of the living SC comprise a persistent metabolic activity (e.g., proteolysis of proteins, cytokine activation, lipid for-

mation, acidification), homeostatic/ metabolic links to deeper cell layers, an external biosensor function (e.g., external humidity has an impact on proteolysis, DNA synthesis and inflammation), and pathophysiologic links to deeper skin layers (barrier abrogation initiates inflammation) [80, 81]. The concept of the stratum corneum functioning as a biosensor to internal and external stimuli implies the existence of signaling mechanisms between the stratum corneum and deeper cell layers. Several processes are stimulated by barrier abrogation (Table 17.1), most importantly (relative to ACD), the activation of cellular signaling via MAP kinases (MAPK) p44/42 MAPK, and p38 MAPK [82], and the release (from preformed pools) and synthesis of several cytokines (Table 17.1). In particular, TNF-α was shown to increase via the TNF receptor p55 and induction of sphingomyelinase activity the synthesis of ceramides [83]. The role of TNF-α as a danger signal in the pathogenesis of ACD is crucial. The inflammatory cytokines remain increased in chronic perturbation, resulting in a cytokine cascade, with downstream stimulation of chemokines, adhesion molecules, and Langerhans cells [59]. Stimulation of class-I nuclear receptors with steroids (glucocorticoids, estrogens, androgens) as ligands may provoke a decline in barrier function or a delay in barrier recovery. The class-II family comprises not only receptors for ligands such as thyroid hormone, retinoic acid, vitamin D3, but also orphan receptors, including peroxisome proliferator-activated receptor-(PPAR-)α (with free fatty acids as natural ligand), PPAR-γ (eicosanoids), PPAR-δ (unknown natural ligand), and LXR-α,β (oxygenated sterols). When activated by, for example, coproducts of the increased lipid synthesis after barrier disruption, namely free fatty acids, they are involved in epidermal growth, differentiation, and barrier function. Furthermore, PPAR-α activation may be involved in an increased synthesis of ceramides and cholesterol derivatives [84], and may have anti-inflammatory effects in irritant and allergic contact dermatitis [85].

Table 17.1. Signals in response to barrier disruption (modified after [81])

Signal	Regulated response
Ions: Ca^{2+}, K^{+}	Activation of p44/42 and p38 MAP kinases [82] Lamellar body secretion Keratinocyte differentiation
Cytokines: TNF-α, IL-1α, β, IL-1Ra, GM-CSF, IL-6, IL-8	DNA synthesis Lipid synthesis (IL-1α)
Growth factors: NGF, TGF-β1,amphiregulin	DNA synthesis
Sterol regulatory element-binding proteins	Cholesterol/fatty acid synthesis LDLr expression
Nuclear hormone receptor: Class I (steroids), class II (PPAR)	Epidermal differentiation Epidermal proliferation Lipid (ceramide and sterol) synthesis) [84] Anti-inflammatory effects in irritant and allergic contact dermatitis [85].

It is hypothesized that the first event after barrier disruption is an increase in transepidermal water loss (TEWL), leading to hypertonicity of epidermal cells and subsequent change in the balance of ions [82]. A number of signals may be involved in the pathogenesis of allergic contact dermatitis as well

17.3 Atopic Eczema and Impairment of the Epidermal Skin Barrier

Although the existence of a defect in skin barrier function in AE is well accepted, whether this defect is innate and pre-exists or whether it is a consequence of chronic cutaneous inflammation, or both, is still being debated. To deal with this controversy, a distinction should be made between function (and the operationalized indicators) and structure and its biochemical/ultrastructural indicators, such as a decrease in total lipids, a different composition of ceramides, and a different epidermal differentiation [75, 86, 87].

The barrier function is most frequently measured as water permeability and water retention by means of the transepidermal water loss (TEWL), and it was shown to be elevated in nonlesional dry skin in AE [88, 89]. It was also shown that the elevated TEWL was confined to patients with active AE [90], correlated with the acuteness of dermatitis, and was said to be normal in completely healed (and not necessarily normal appearing) skin [90, 91, 92]. However, after epidermal insults through solvents, irritants, and surfactants, TEWL increases – less in healthy controls, slightly more in inactive AE and dry skin, and significantly more in active AE – indicating an increased susceptibility of barrier function to irritants like sodium lauryl sulfate (SLS) [89, 90]. However, AE is a less reliable marker of susceptibility than TEWL itself [93, 94], indicating only

a moderate correlation between AE and the generally used TEWL as a measure of permeability. It would certainly be premature to generalize the findings of an impaired barrier to only one single molecule (water) to other compounds, and additional work will be needed to explore whether TEWL serves as a universal, accurate, and reproducible predictor for transdermal penetration of xenobiotics. Supporting this notion, when using caffeine and lidocaine as model permeants, the extent of changes in TEWL correlated linearly with transdermal penetration of both drugs [77]. The concept of a (more or less) general barrier impairment of atopic skin could be supported further: it was shown that the skin barrier defect in AE extends to other substances such as dimethyl sulfoxide and theophylline [95]. Finally, larger protein molecules like inhalant allergens of the atopy patch test and natural latex proteins can penetrate into the skin of AE patients [66, 96]. An important prerequisite for proteins to penetrate into the skin seems to be the enzyme activity exhibited at least by some protein allergens [56]. The allergens of house dust mites, for example, are proteolytic enzymes which are able to increase permeability. The molecular targets of the Der p are occludines, members of the claudin family (transmembrane proteins of the tight junctions) [56]. And in fact, the barrier function was seriously disturbed in atopy patch test reactions, in contrast to contact allergic patch test reactions. Altogether, these findings may be taken as hints on a more general, inherent barrier impairment of atopic skin, which in turn may be further enhanced in a vicious circle by aeroallergens allowing the penetration of further allergens [97].

Beyond a simple mechanistic view of a window more or less open, substantiated by the different morphology and biochemistry of the atopic skin, the penetration could differ in a biochemical aspect as well, depending on the biophysical properties of the allergen. Substances with, for example, a specific partition coefficient (log P) could be "attracted" by the differing lipid composition of atopic skin, and "rejected" (or less attracted) by the lipids of normal skin, and vice versa. Based on such purely theoretical assumptions, it would be difficult to establish a general rule on the penetration of xenobiotic compounds in AE. Regardless of a different or similar immunologic processing of contact allergens, the susceptibility to sensitization to specific compounds could be different in AE, due to a different, allergen-specific penetration behavior.

17.4 Immunologic Mechanisms in Allergic Contact Dermatitis

The immunology of ACD has classically been divided into sensitization and elicitation phases. The sensitization phase (also called the induction phase) refers to those events that lead up to the activation of T lymphocytes, whereas the elicitation phase is the term applied to events that occur once activated T cells are re-exposed to the same allergen.

17.4.1 Sensitization Phase

Sensitization begins with the entrance of haptens into the skin [98–100]. Those haptens participating in the induction phase conjugate to epidermal and dermal molecules, generally referred to as hapten-carrier complex. The critical binding structures have not yet been identified unequivocally. Probably depending on their chemical nature, haptens may bind directly to peptides bound on MHC molecules of antigen-presenting cells, or bind to proteins, which are processed by antigen-presenting cells, or bind directly to MHC molecules. Sensitizing organic compounds are generally electrophilic and bind covalently to nucleophilic groups, such as thiol, amino, or hydroxyl groups, whereas metal ions, e.g., nickel cations, form stable metal–protein chelate complexes [101]. However, some xenobiotics (prohaptens) only enter these first steps of sensitization after conversion to protein-reactive haptens, i.e., the original compound is a nonsensitizer. Examples are limonene and colophony. Their induction capacity relies on oxidation by air [102, 103]. In addition, xenobiotic metabolizing enzymes in the skin can convert prohaptens to electrophilic compounds [104, 105]. One example is the activation of cinnamic alcohol to the presumed allergen cinnamic aldehyde [106]. For effective sensitization, a chemical must therefore be inherently protein-reactive or must be converted in the skin to a protein-reactive metabolite. For the latter compounds, genetic differences in metabolism may play a role in the differential susceptibility of individuals to develop contact allergy [107, 108].

17.4.1.1 Activation, Maturation, and Migration of Langerhans Cells

Immature dendritic cells (DCs) bearing the antigen are first activated by antigen nonspecific stimuli, (as irritants also activate LCs). Following activation, these cells are stimulated to leave the epidermis and migrate to the local lymph node. During migration, LCs undergo functional maturation such that they lose the ability to process antigen and acquire instead the characteristics of mature antigen-presenting DCs, e.g., increased expression of MHC and of costimulatory molecules (ICAM-1, LFA-3, B7-1, and B7-2) [109].

The whole process is orchestrated by several important changes in the skin, involving cytokines and chemokines and their receptors (IL-1β, TNF-α, IFN-γ, IP-10, MIP-2, IL-12, IL-15, IL-18), adhesion molecules (E-cadherin, ICAM-1, α6 integrin, CD44 variants), lipid mediators(PGE2), and matrix metalloproteinases (e.g., MMP-9) [100–112]. The first and probably most crucial step in the induction phase is the early upregulation of IL-1β mRNA and synthesis of the IL-1β precursor, which is cleaved by the protease IL-1β-converting enzyme (ICE; caspase-I). Caspase-I activation is induced either by haptens or irritants (SLS) [113]. IL-1β was also referred to as the master cytokine, as it was able to initiate the whole cytokine profile, in particular TNF-α synthesis by adjacent keratinocytes, and second, to supply signals for the activation, maturation, and mobilization of LCs [114]. TNF-α provides LCs with the second cytokine signal necessary for successful migration. These stimuli are delivered to LCs via both types of the TNF-α receptor (p55 TNFR and p75 TNFR) [115], and the type 1, signal-transducing, receptor for IL-1, IL-1RI [116]. Furthermore, IL-1β and TNF-α weaken and break the E-cadherin bonds that bind LCs to adjacent keratinocytes, thereby allowing LCs to move through the layers of the epidermis. To facilitate the penetration of LCs into the dermis, the production of several matrix metalloproteases is upregulated (by TNF-α), which participate in the degradation of E-cadherin and degrade the macromolecules of the epidermal basement membrane [109]. The movement via the extracellular matrix and lymphatic endothelial cells is guided by several chemokines and their respective receptors (e.g., CCR 7) [111].

Mobilization and migration of LCs seem, however, subject to counter-regulatory influences[110]. One important candidate is IL-10, which is upregulated following skin sensitization. It has been suggested that in the absence of IL-10 (in IL-10 knockout mice) the proinflammatory cytokines IL-1β and TNF-α are overexpressed. Another cytokine that may have the potential to regulate LC migration is TGF-β1, which is able to inhibit the upregulation by TNF-α of CCR7 expression on DCs and to increase the expression by DCs of E-cadherin [117]. As further regulators of LC migration, lactoferrin (LF) and peroxisome proliferator-activated receptor γ (PPAR-γ) can be mentioned. LF is an iron-binding protein, which is found in exocrine secretions, known to be expressed in healthy skin. Exogenous topical (recombinant) LF was shown to be able to inhibit allergen-induced LC migration, secondary to suppression of the de novo synthesis of TNF-α, and possibly of other proinflammatory cytokines [116, 118, 119]. PPARs belong to the nuclear hormone receptor superfamily [120]. PPAR-γ is involved in macrophage maturation and modulation of immune and inflammatory reactions [120, 121]. Recently, it was shown that LCs express PPAR-γ and that activation of PPAR-γ by rosiglitazone, an antidiabetic drug acting as a synthetic ligand, specifically impairs the departure of LCs from the epidermis [122].

17.4.1.2 The Role of (Nonspecific) Inflammation

In many instances, it appears that topical administration of a contact allergen alone is sufficient to trigger the induction or upregulation of those cytokines necessary for the effective acquisition of sensitization. Under these conditions of exposure, the chemical itself causes sufficient cutaneous inflammation and irritation and hence the production of proinflammatory cytokines. However, chemicals that do not provoke proinflammatory changes may fail to induce the necessary cytokine responses. Furthermore, endosomal processing (MHC peptide ligand formation) and LC activation depend on inflammatory stimuli [123, 124]. The intimate relationship between irritation and sensitization was substantiated by, for example, studies with the contact allergen DNCB together with the irritant SLS in mice [125]. At high (irritant) doses of DNCB, SLS did not influence the levels of immune activation induced by the allergen. However, at lower (nonirritant) concentrations of DNCB, responses were augmented by SLS, which is thought to provide the necessary exogenous inflammatory stimuli. Coadministra-

tion of an irrelevant hapten reduced the doses still sufficient to elicit CA by a factor of 10^3 [126]. It was proposed that the chemical irritancy of a hapten activates the innate immune system, an activation step necessary for development of specific immunity in the skin [127] (The innate immune response is a defense mechanism through which invariant molecular patterns of infectious agents – Toll-like receptors – are recognized [128]).

The concept referring to the necessary danger signals [129] is supported by clinical observation. Patients with a lower threshold of sensitivity to SLS seem to be more susceptible to sensitization to a contact allergen (colophony) [130]. In summary, a certain level of skin irritation seems to be required, at least for weak allergens. Chemicals that fail to trigger sufficient local cytokine production may – in the absence of additional exogenous stimuli – be unable to realize their full potential as allergens.

17.4.1.3 Langerhans Cell–T Cell Interaction and the Role of T Cell Subsets

The induction of skin sensitization and the subsequent elicitation of allergic contact dermatitis depend on the development of hapten-specific T lymphocytes.

Primary hapten presentation to naive T cells together with costimulatory signals results in the generation of cutaneous hypersensitivity (CHS) effector cells. In contrast to other types of delayed-type hypersensitivity (DTH) responses, which are mediated by CD4+ cells, most haptens evoke a response consisting mainly of CD8+ effector cells. However, besides CHS effector cells, T cell populations that downmodulate CHS are also induced, namely hapten-specific suppressor cells. Reduction of the hapten dose results in gradual loss of T suppressor cell induction but retained sensitization. Further dose reduction finally results in low-zone tolerance [131, 132]. This dose-dependent activation of different T cell subsets might result from different antigen presentation. Whereas insufficient antigen-presenting cell (APC) activation or inadequate costimulation results in T cell anergy, inadequate ligation of T cell receptors may result in generation of T suppressor cells. High doses of hapten may lead to antigen presentation by LCs and also by less efficient APCs, the latter generating only inadequately primed T suppressor cells. Lower doses of hapten might result in antigen presentation exclusively by LCs, and therefore induce CHS effector cells only. Very low doses might result in suboptimal hapten concentration, even on professional APCs (LCs) [126], or bypass the involvement of LCs [132], again generating T suppressor cells that mediate low-zone tolerance, which were characterized as CD8 helper-type 2 cells [133].

For activation and proliferation, T cell receptor triggering (signal 1) is insufficient, but hapten-presenting APCs also provide the required costimulation (signal 2), which involves, for example, IL-1α, OX40 ligand, and cellular adhesion molecules (e.g., CD80 and CD86) [134–136]. The latter molecules bind to their counterparts on T cells, CD28, and CD152 (CTLA-4, functioning as a negative regulator [137]). These interactions promote mutual activation of both hapten-presenting APCs and hapten-reactive T cells. To promote T cell proliferation, cellular adhesion stimuli need to be complimented by several cytokines (e.g., IL-2, a highly potent T cell growth factor). Primary skin contact with most contact allergens leads to differentiation and expansion of allergen-specific effector T cells, particularly CD8-positive cells displaying the type-1 cytokine profile, whereas a subgroup of CD4-positive T cells produces IL-2, IL-4, and large amounts of IL-10, regulating the immune reaction principally mounted by CD8-positive T cells. However, prolonged allergenic contact ultimately leads to a predominance of type-2 allergen-specific T cells, which may take over the role of type-1 cells in causing contact allergic hypersensitivity. It seems likely that the expression of IL-4 (and possibly other type-2 cytokines), particularly at sites of dermal challenge, regulates what is considered to be a largely Th1- or Tc1-dependent immune response, although the factors governing whether it is upregulated or downregulated are still unclear [138–140]. Finally, on maturation T cells acquire (in an IL-12-dependent manner) molecular keys that allow extravasation, one of the important ones being CLA, the (cutaneous lymphocyte associated antigen), which is formed from the glycosylation of P-selectin glycoprotein ligand 1.

17.4.2 Elicitation Phase

The elicitation phase of ACD is triggered by re-exposure of the skin to the relevant hapten. As in the induction phase, antigen-presenting cells are required to reactivate specific T cells [126, 98, 100].

17.4.2.1
The Movement of Nonspecific and Specific T Cells to the Site of Hapten Re-exposure

The first events initiated by the hapten in the skin after contact with keratinocytes are nonspecific inflammatory reactions caused by inherent inflammatory/irritant properties of the hapten (danger signals). Inflammatory and vasoactive mediators from, for example, mast cells (C5a and serotonin), cytokines (TNF-α, IL-1α, GM-CSF, IL-18, from keratinocytes, and later from infiltrating monocytes and DCs), and chemokines (CXCL1, MCP1 [CCL2], RANTES [CCL5], Mig [CXCL9], CTACK [CCL27], IP-10 [CXCL10], MIP3-α [CCL20]) are released, which is followed by an activation of endothelial cells and an increased expression of adhesion molecules. All these first inflammatory responses are nonspecific, due to the inherent proinflammatory properties of the hapten (or accompanying inflammatory stimuli). Nonspecific leukocyte recruitment is largely under the control of chemokines, released in a sequential and coordinated manner from resident and immigrating cells [111]. As the hapten can only be presented in the extravasal tissue, T cells have to move from circulation to the hapten-exposed regions. The process is initiated by selectins expressed on T cells (L-selectin), endothelial cells (P-selectin and E-selectin) and activated platelets (P-selectin). Selectins form bonds between endothelial surfaces and T cells, moderating the rapid motion of T cells to a slow roll ("tethering"). In a second stage of extravasation, T cells receive chemokine signals, which are required for integrin activation. Integrins bind to ICAM-1 and VCAM-1, which halts T cell motion. Now cell extravasation into the dermis and migration to the site of the hapten are possible.

17.4.2.2
Specific T Cell–Antigen-Presenting Cell Interaction and Inflammatory Response

The accumulation of mostly nonspecific and much less specific T cells on the site and their activation by APCs, macrophages probably playing a key role [141], is followed by the release of various cytokines (IFN-γ, TNF-α, TNF-β, GM-CSF, IL-1). The main effector cytokine in ACD is IFN-γ, acting in concert with TNF-β to upregulate the expression of ICAM-1 [100]. Another cytokine, IL-12, was shown to be important in the induction and the elicitation phase of ACD. The cytokines in turn stimulate keratinocytes to produce IP-10, Mig, and I-TAC (CXCL11), the ligands for CXCR3. These chemokines selectively attract T lymphocytes. Keratinocytes continuously produce large amounts of CXCR3 ligands, thus contributing to further accumulation of CXCR3-bearing T cells. The result is that more than 70 % of ACD-infiltrating T cells are CXCR3+. Mast cells and thrombocytes are activated and enhance the inflammatory reaction. The final steps are, therefore, as the first steps of elicitation, nonspecific inflammatory processes.

17.4.2.3
The Effector T Cells

Effector T cells may be CD4+ (Th) or CD8+ (Tc) cells. CD8+ cells producing IFN-γ, no IL-4, and no IL-10 (Tc1 cells), and activated under the influence of IL-12 [142 – 144], are now considered to be the main effector cells in contact allergy, together with some (IFN-γ-producing) CD4+ cells, but other CD4+ cells (producing IL-4 and IL-10 but no IFN-γ) mainly seem to have a regulatory function. It seems now established that both CD4+ (Th1) and CD8+ (Tc1) cells are necessary for the full expression of ACD [145]. Furthermore, the inflammatory reaction in CHS depends on CD8+ cytotoxic activity mediated by perforin and FasL [146] and is responsible for the lysis of keratinocytes [147 – 149]. Beside CD8+ cells, CD4+ cells in concert with IFN-γ may also exert cytotoxic activity [143]. It was further hypothesized that CD8+ T cells lyse CD4+ cells (bystander cytolysis), responsible for the predominance of CD8+ effector T cells [147]. However, an increased apoptosis of Th1 cells was observed only in atopic patients (leading to a predominance of Th2 cells), and not in ACD patients [150].

T cell subsets, whether CD4+ or CD8+, release not only type-1 cytokines (IFN-γ, IL-12), an opinion held for a long time, but also type-2 cytokines, particularly IL-4 [151, 152]. Loss of IL-4 expression in BALB/c mice was associated with impairment of the ACD reaction to DNCB. On the other hand, Ni-specific T cell clones prepared from nonallergic patients displayed low IFN-γ and a high IL-10 production, compared with T cell clones from allergic patients, again indicating a regulator role for IL-10 on an individual basis [153]. With regard to the regulation of the balance between these two responses, it is likely that the properties of the allergen play the major role in controlling the equilibrium between Th1 and Th2. The response to DNFB is

Th1-predominant, the contact allergen MCI/MI elicits, as metals, a mixed (Th1 and Th2) profile [154], whereas the fluorescein isothiocyanate response is Th2-predominant.

17.4.2.4 The Resolution of Allergic Contact Dermatitis

The elicitation phase of ACD is self-limiting. IL-4 and IL-10, secreted in the late elicitation phase by CD4+ Th2 cells, have both been implicated in its downregulation. T regulatory (Tr) lymphocytes producing predominantly IL-10 may play a central role [143]. They migrate in response to various chemokines including I-309 (CCL1), MCP-1, MIPs, and TARC. Tr cells express higher levels of CCR8 (the receptor of I-309). I-309 from keratinocytes and activated T cells with an earlier kinetics than IL-4 and IL-10 attracts Tr cells more vigorously than Th2 cells. This indicates that I-309/CCR8 may contribute relevantly to the termination of ACD through the recruitment of Tr lymphocytes [111]. IL-10 blocks DC maturation, including IL-12 release, thus impairing activation of T cells. In addition, the release of factors such as PGE2 and TGF-β, derived from activated keratinocytes and leukocytes, contributes to dampening the immune response. PGE2 inhibits the production of pro-inflammatory cytokines, probably through an enhanced production of thrombospondin1, an endogenous antiinflammatory regulator stimulated by nonspecific danger signals and released by DCs [155]. TGF-β silences activated T cells and inhibits further infiltration by downregulating the expression of adhesion molecules on endothelial and skin cells. Further suppressive effects were observed with certain neuropeptides, especially α-MSH and VIP (in contrast to other neuropeptides such as substance P and CGRP, which enhance the inflammatory response) [156, 157].

17.5 The Immunopathogenesis of Atopic Eczema – Possible Interference with Allergic Contact Dermatitis

17.5.1 Background

AE is a chronic eczematous skin disorder with a complex polygenetic background that occurs as cutaneous manifestation of the atopy syndrome. Accordingly, the majority of patients with AE show high levels of IgE antibodies, which usually react with a limited spectrum of typical allergens, such as food components, house dust mite, or birch pollen, and many patients suffer from concomitant allergic rhinoconjunctivitis or asthma. A significant percentage of affected individuals, however, do not show IgE hyper-responsiveness. These patients, who are usually referred to as "intrinsic" or "nonallergic" AE patients, might be genetically and immunologically different from "extrinsic" AE patients [158, 159], although some principle mechanisms, such as the activation of IL-5- and IL-13-producing CD4+ and CD8+ T effector cells, appear to be comparable [160].

IgE-related inflammatory pathways were originally thought to play a critical role, especially in immediate-type hypersensitivity reactions (type I) with (contact) urticaria as a typical skin symptom. Because AE clinically and histologically corresponds to a cutaneous DTH response (type IV), and AE lesions are in fact often indistinguishable from those of ACD, the role of IgE in this type of atopic skin lesion has long been theoretical. A possible link between the increased production of IgE antibodies and the development of eczematous skin lesions has been provided by the demonstration of high levels of high-affinity IgE receptors, FcεRI, on epidermal dendritic cells of AE patients, and the finding that these molecules contribute to a preferential and highly efficient uptake of IgE-targeted allergens and subsequent activation of specific T cell responses, the latter step resembling the sensitization phase of ACD. The highest levels of FcεRI expression have been observed on a subset of epidermal DCs, the so-called inflammatory epidermal dendritic cells (IDECs), which seem to be specifically recruited into the epidermis of active AE lesions and might contribute to the increased number of epidermal DCs observed in this condition [161]. Upon activation, these cells release large amounts of pro-inflammatory cytokines, thereby possibly amplifying the inflammatory immune reaction in AE [159]. Because aggregation of FcεRI on monocytes and DCs induces NF-κB activation [162], increased expression of this receptor may directly contribute to abnormal APC function in AE.

In both types of eczematous skin disease, AE and ACD, activated T cells have been identified as the main effector cell type. According to current pathogenetic concepts, however, a characteristic feature of AE is the preferential activation of CD4+ and CD8+ T cells that

produce Th2 cytokines, such as IL-4, IL-5 and IL-13 [163], while the majority of ACD reactions, under the influence of IL-12 derived from APCs and other cell types, involve the activation of the Th1 and Tc1 subsets with IFN-γ as the leading cytokine [164], although some ACD responses may also require the activation of Th2 cells. The bias toward activation of Th2-type pathways is regarded as a principal immune deviation in AE, which is likely to result from complex interactions between genetic and environmental factors. The preferential priming of Th2 cells in AE, which is reflected in the preponderance of (allergen-specific) Th2 cells in the peripheral blood, acute skin lesions, and the early phase of atopy patch test reactions, is likely to occur as the consequence of several abnormalities present at different cellular and molecular levels of the immunologic cascade. On the other hand, a lack of sufficient Th1-inducing stimuli during a critical learning phase of the immune system in early childhood has been postulated as an important environmental component involved in the impaired ability of patients with atopic diseases to generate allergen-specific Th1 responses. In line with this concept, changes in the infectious environment and in the pattern of microbial exposure of children associated with westernization might be a critical factor underlying the increased prevalence and severity of atopic diseases that has been observed in Western countries over the last decades (the hygiene hypothesis) [165, 166].

17.5.2 Immune Deviation in Atopic Ecezma

The presently available experimental data on the possible mechanisms involved in the preferential generation and recruitment of Th2 cells and induction of skin inflammation in AE have recently been reviewed [167, 165]. They may be summarized as follows:

1. Keratinocytes in AE show different abnormalities including overexpression of thymic stromal lymphopoietin (TSLP). TSLP activates DCs and induces the expression of chemokines that selectively attract CCR4-expressing Th2 cells such as TARC (CCL17) and MDC (CCL22). Moreover, TSLP-primed DCs induce IL-4, IL-5, IL-13, and TNF-α in responding T cells, but downregulate IFN-γ and IL-10 [168]. There is also evidence that, in addition to an exaggerated expression of Th2-selective chemokines [169, 170] and other chemotactic factors involved in the recruitment of DCs and T cells, such as MIP-3a (CCL20) [171, 172] and CTACK (CCL27) [173], keratinocytes in AE patients, compared with nonatopics, release higher amounts of pro-inflammatory cytokines, including IL-1 and TNF-α, either spontaneously or in response to stimuli such as IFN-γ [174, 175]. The higher baseline activation of keratinocytes may be related to the disturbed epidermal barrier function in AE. Alternatively, a state of keratinocyte preactivation could result from endogenous abnormalities regarding the inhibitory effects provided by cytokines such as TGF-β [176, 177, 178, 214), a product, for example, of T cells with suppressor functions, and other negative regulators of IFN-γ signaling, including members of the suppressor of cytokine signaling (SOCs) family [179]. Finally, increased keratinocyte apoptosis in AE may trigger the release of several factors that induce chemotactic responses in CXCR3-expressing T cells, which are highly increased in AE lesions [180].
2. At the level of APCs, including monocytes and monocyte-derived DCs, several functional alterations have been described in AE patients, including an increased immunostimulatory capacity [181] with preferential induction of Th2 cells [182]. This finding is possibly related to a reduced capacity to secrete IL-12 and increased release of IL-10, at least under certain conditions of DC activation [183]. Furthermore, monocyte-derived DCs from AE patients display an enhanced production of chemokines such as MDC (CCL-22) [184] and IL-16 [185], a cytokine involved in the selective recruitment of CD4+ T cells, DCs, and eosinophils. The results of other studies indicate a defective synthesis of the Th1-activating cytokine IL-18 in monocytes of AE patients as a possible mechanism underlying decreased IFN-γ production in response to bacterial toxins [186, 187].
3. Th1 and Th2 cells develop from the same naïve T cell under the influence of various factors, the majority of which are active during the interaction with APCs. These include ligation of the T cell receptor, binding of costimulatory molecules, and presence of regulatory cytokines in the micromilieu of the responding Th cell. The functional balance between Th1 and Th2 cells in a given immune response will also depend on the presence of regulatory T cell subsets that may specifically suppress one

or the other Th subset, either via release of mediators or the selective induction of T cell apoptosis. Notably, a preferential apoptosis of circulating Th1 memory effector cells has recently been shown to contribute to the predominance of Th2 cells in atopic diseases [150]. Signals through contact molecules, as well as through cytokine receptors, induce a complex series of secondary molecular events that ultimately lead to the binding of cell type-specific transcription factors to regulatory elements in the promoters of sets of genes implicated in the functional program of the activated T cell. These signal transduction cascades have recently been identified to play an important role in determining Th1 or Th2 differentiation because of their possible antagonism [165]. At the molecular level activation of STAT6, the proto-oncogene c-Maf and GATA-3 are associated with Th2 development. GATA-3 not only plays a role in the upregulation of the Th2 cytokines IL-4, IL-5, and IL-13, but also inhibits the production of IFN-γ, thereby preventing Th1 development [188]. While the interaction of IL-4 with its receptor on the surface of naïve T cells initiates the activation of STAT6, binding of IL-12 to the IL-12R results in the activation of STAT4. Another transcription factor involved in Th1 lineage commitment and expression of IFN-γ is the protein T-box expressed in T cells (T-bet), which simultaneously represses IL-4 and IL-5 [188]. While there is solid evidence for a Th2 polarization, the exact relation between altered signaling cascades and the immune deviation in AE is less clear. However, from animal models it can be concluded that the activity of transcription factors may play a crucial role in the manifestation of atopic diseases including AE [189; 190].

4. There is no doubt that T regulatory cells (Treg) are important elements in maintaining a physiological immune homeostasis of the skin, and a disturbance of Treg functions may contribute to abnormal immune responses underlying AE and ACD. Treg cells have been divided into natural and adaptive subpopulations [191]. The former are generated in the thymus and later migrate to peripheral tissues, where they normally function to prevent the activation of self-reactive T cells that have the potential to develop into effector cells. They are characterized by a CD4+CD25+ phenotype, expression of Foxp3 and glucocorticoid-induced TNF receptors, produce little or no cytokines, and mainly act through T cell-T cell or T cell-APC contact-dependent mechanisms. Among CD4+ cells, Th3 cells, which mainly produce TGF-β, and Tr1 cells, which mainly produce IL-10, with or without TGF-β, are adaptive Treg cells that also originate from the thymus but differentiate further and acquire their suppressive activity in the periphery under certain conditions of antigenic stimulation [191]. Their expression of CD25 is variable, and their mechanism of suppression is mediated by inhibitory cytokines, such as IL-10 and TGF-β. Natural and adaptive Treg cells might function in different immunologic settings, depending, for example, on the context of antigen exposure and the nature of the inflammatory response. Whether Th1 and Th2 responses are equally susceptible to the suppressive activities of Treg cells, and whether they are controlled by the same or different types of Treg cells is presently not completely clear. There is evidence to suggest that CD4+CD25+ Treg cells effectively suppress Th1 responses, but have an impaired suppressive [192] or even activating effect on Th2 responses [193]. In fact, a recent study found an increased frequency of CD4+CD25+ Treg cells in the peripheral blood of AE patients compared to patients with asthma and healthy controls [194]. The authors also suggested that stimulation of CD4+CD25+ Treg cells with staphylococcal superantigens may reverse their suppressive function. Furthermore, IL-10, a central mediator of adaptive Treg cells, has been implicated in the control [195] as well as in the induction of Th2 allergic reactions [196].
5. It is noteworthy that in chronic AE lesions, the expression of IL-4 and IL-13 decreases, whereas expression of IFN-γ is upregulated. The switch toward a Th1-type response is probably mediated by an increased dermal recruitment of eosinophils, macrophages, and DCs expressing IL-12, and chemokines derived from keratinocytes in chronic AE lesions may further enhance the local accumulation of Th1 cells (reviewed in [164]). IL-4 itself and the increased colonization of AE skin by *Staphylococcus aureus* may represent important stimuli that activate DCs and macrophages to release IL-12. The microbial induction of toll-like receptors may also initiate other events in favor of a Th1-type response, including the inhibition of Th1-suppressing Treg cells and upregulation of T-bet, which are able to convert polarized Th2 cell into IFN-γ-producing

Th1 cells. Thus a variety of changes in the local microenvironment may finally lead to a cutaneous cytokine milieu reminiscent of ACD that promotes the activation of cytotoxic lymphocytes. Interestingly, in a certain analogy to ACD, a T cell-mediated apoptosis of keratinocytes has recently been proposed as a pathogenic mechanism in AE [148].

17.5.3 How Atopic Eczema Can Affect Allergic Contact Dermatitis

Because AE was regarded as a Th2-type disease, contrary to Th1-driven ACD, a lower prevalence of ACD reactions in AE patients compared to healthy controls was expected. On the other hand, the local microenvironment in AE, particularly that of chronic AE lesions, may be generally regarded as a so-called danger signal that should facilitate the development of ACD response to an absorbed allergen. However, recent epidemiologic studies suggest that ACD is about as common in AE patients as it is among nonatopic individuals. Based on the increasing knowledge of the specific immunologic abnormalities in AE, interactions with the pathogenesis of ACD may hypothetically occur at multiple levels (Table 17.2). Among others, these include:

- The increased release of chemokines and cytokines from keratinocytes
- The presence of high numbers of preactivated DCs that are able to secrete large amounts of chemotactic and pro-inflammatory mediators
- The presence of increased numbers of activated memory effector and cytotoxic T cells
- Changes in the local control of inflammatory responses by Treg cells

The specific immunologic changes associated with AE may either facilitate or hamper the development of ACD responses, depending on the type of AE (intrinsic vs extrinsic) [197, 159], the duration of AE skin lesions (acute vs chronic), the presence of co-factors, such as epidermal barrier dysfunction (dry skin) and microbial colonization (*S. aureus*) and the type of the potential contact allergen (Th1- or Th2-type ACD). Clearly, the exact consequences of different immunologic alterations present in AE for the manifestation of ACD reactions remain to be determined. It is also possible that ACD reactions to a given allergen differ immunologically between AE patients and nonatopic individuals, as suggested by recent studies on the cutaneous response [49] and the release of cytokines from peripheral blood nuclear cells to nickel in patients with ACD to nickel with or without concomitant AE [50].

17.6 Conclusion

Susceptibility to sensitization to contact allergens may vary with the clinical severity of AE [7, 198, 199, 200], e.g., has been found remarkably low in patients with high serum IgE levels (above 1,000 kU/l [21, 35]. Furthermore, the group of patients with AE has been found to be heterogeneous concerning responses to immediate type hypersensitivity allergens (extrinsic vs intrinsic type of AE); such heterogeneity, albeit not yet clearly identifiable, may also exist with regard to contact allergens, both specifically in AE patients and generally. Possible mitigating effects of AE on the pathogenic process of ACD on the immunological level may be compensated by the established barrier dysfunction, facilitating the penetration of haptens in AE. In summary, taking recent evidence into account, it appears reasonable to assume a largely similar susceptibility to CA in persons with or without AE.

Table 17.2. Preimmunologic and immunologic factors that may interfere with allergic contact dermatitis in atopic eczema

	Atopic eczema	Possible (hypothetical) effect on ACD in AE
Preimmunologic parameters	Disturbed epidermal barrier function: TEWL increased in nonlesional dry skin [88, 89]; permeation of drugs [77, 95] and macromolecules [66, 96] (increase)	Penetration of an allergen into the skin facilitated, possibly also haptens with a mol weight > 500 D
	Biochemical: different lipid composition [75]	Different permeation of the hapten depending on its biophysical properties (e.g., log P)
	Repair signals also acting as inflammatory signals (e.g., TNF-α) [81, 83]	Danger signals in the immunology of ACD

(Abbrevations see p. 193)

Table 17.2. (cont.)

	Atopic eczema	Possible (hypothetical) effect on ACD in AE
Immunologic parameters	**Keratinocytes** Increased MMP activity with increased serum levels of TIMP-1 that resolve during treatment [201]	Increased sensitivity of keratinocytes to activation by allergen contact
	Altered caspase activation probably due to genetic variations in the caspase recruitment domain containing protein 15 (CARD15) [202]	
	Animal model: evidence for a crucial role of increased caspase-1 activity [203]	
	Indirect evidence for an altered pattern of toll-like receptors [204]	Modulation of cutaneous immune responses
	Evidence for an increased cytokine response (including IL-1, TNF-α) of keratinocytes from healthy-appearing skin after stimulation with IFN-γ [174] and in response to topical application of irritants (SDS)/allergens (HDM) [175]	Enhanced keratinocyte-driven stimulation of epidermal DC
	Decreased levels of IFN-γ inhibiting transcription factors SOCS1, 2, 3 in lesional AE [179]	
	Increased production of TARC/CCL-17 and MDC/CCL-22 [205] possibly mediated by IFN-γ [169] and inhibited by TGF-β [176]	Augmented attraction of T cells to sites of allergen challenge
	Overexpression of human thymic stromal lymphopoietin (TSLP): activates DC and induces the expression of chemokines (TARC/CCL17 and MDC/CCL22) that selectively attract Th2 cells; TSLP-primed DC induce IL-4, IL-5, IL-13, and TNF-α in responding T cells, but downregulate IFN-γ and IL-10 [168]	The Th2-attracting milieu in acute lesions may negatively affect certain types of ACD reactions
	Increased keratinocyte apoptosis resulting in the release of several factors that are overexpressed in AE lesions and attract CXCR3+ T cells [180]	
	Antigen-presenting cells: dendritic cells, monocytes/macrophages Increased stimulatory capacity of MoDC from atopic donors [181] with enhanced induction of Th2 responses in T cells from atopic donors [182]	Factors that facilitate DC migration and DC-dependent T cell activation may trigger the manifestation of ACD
	Increased production of IL-10 but decreased production of IL-12p40 from MoDC of AE patients after LPS stimulation [183] with IL-10 being a central mediator in the induction of Th2 responses and eosinophilia in a murine model of AE [196]	Preferential stimulation of Th2 cells may antagonize ACD
	Disturbed maturation of MoDC in response to CD40 cross-linking [183]	
	IDEC, a subpopulation of inflammatory epidermal DC with very high expression of FcεRI, are selectively recruited into the epidermis; upon ligation of FcεRI, IDEC secrete IL-1α, IL-1β, MCP-1, MCP-3, RANTES TNF-α, and MIP-1α [161]; preactivation of DC might be related to induction of NFkB signaling following ligation of FcεRI [162]	
	Increased expression of IL-16 in epidermal DC in active lesions and positive atopy patch test reactions, possibly induced by engagement of FcεRI [206, 185] Strong expression of MDC (CCL22) in cutaneous DC [184]	DC-derived lymphocyte-attracting factors may augment ACD responses
	Effector T cells and cytokine milieu Increased numbers of CD4+ and CD8+ T effector cells with increased expression of Th2 cytokines (IL-4, IL-5, IL-13) and IL-10 in acute skin lesions compared with the skin of healthy individuals, but predominance of Th1 cytokines (IFN-γ) in chronic lesions; cytokine switch is likely to occur under the influence of IL-12 released from DC and macrophages (stimulated by IL-4, bacterial antigens) and eosinophils [164]	A pro-inflammatory cytokine milieu (chronic lesions) established by skin infiltrating cells may act as danger signal and trigger ACD reactions Decreased capacity to mount Th1 responses and preferential attraction of Th2 cell may prevent ACD

Table 17.2. (cont.)

	Atopic eczema	Possible (hypothetical) effect on ACD in AE
Immunologic parameters	Comparative DNA microarray analysis shows overexpression of MCP-4 (CCL-13), PARC (CCL-18), and CTACK (CCL-27) in AE vs psoriasis [207] Several studies indicate specifically elevated serum/plasma levels of Th2-selective chemokines TARC (CCL17), MDC (CCL22), and CTACK (CCL27) and correlation of these markers with disease severity [208, 209, 210]; elevated serum levels of IL-16 [211] Increased expression of CCR3 and CCR4 in (acute) lesions, the receptors for the eosinophil/Th2-recruiting chemokines TARC (CCL17) and MDC (CCL22) [212, 170] *Extrinsic vs intrinsic* Comparative RT-PCR analysis indicates three groups of cytokines: IL-1β, IL-5, and IL-13 are increased in AE compared to healthy skin and higher in extrinsic than in intrinsic forms; IFNγ, IL-12, GM-CSF, IL-4, IL-10 are higher in AE compared to healthy skin with similar levels in extrinsic and intrinsic forms; decreased levels of TNF-α in both AE variants compared to healthy controls [158] *Acute vs chronic* In addition to the Th2/Th1 switch: TGF-β is enhanced in acute and even more in chronic lesions; IL-17 is increased in acute lesions, IL-11 increased in chronic lesions [213]; it is unclear how these findings correlate with: – TGF-β suppresses AE-like skin lesions in an established mouse model of AE [177] – TGF-β+/CD4+ T cells suppress Th1- and Th2-mediated allergen-induced skin inflammation in animal models [178] – AE is associated with a low-producer TGF-β1 cytokine genotype [214]	
	T regulatory cells Role of Treg subpopulations and related cytokines (IL-10, TGF-β) remains to be explored; increased expression of IL-10 and TGF-β have been reported; however, IL-10 may enhance certain mechanisms of allergic inflammation (see text); natural CD4+ CD25+ Treg cells seem to be increased in AE, their suppressive effects may, however, be restricted to Th1 cells; bacterial products may break anergy of these cells [194]	High numbers of Treg cells may counterbalance ACD responses Disturbed expression of anti-inflammatory cytokines (IL-10), that physiologically antagonize ACD, may also influence ACD
	Adhesion molecules Variable upregulation of VCAM-1 on dermal DC and endothelial cells [215] Strong expression of ICAM-3 on CD1+ epidermal and dermal DC [216] Overexpression of α6-integrin in active lesions and ACD reactions in AD patients [217]	Increased expression of adhesion molecules may trigger the influx of inflammatory cells in ACD
	Neuropeptides Evidence for an increased number of substance P (SP) and calcitonin gene-related peptide positive fibers [218]; increase in plasma levels of SP and NGF correlate with disease activity [219]; SP might aggravate AE by increasing the production of TNF α and IL-10 rather than by affecting IL-4 and IFN-γ [220]	Neurogenic inflammation may contribute to the manifestation of ACD

ACD allergic contact dermatitis, *APC* antigen-presenting cell, *AE* atopic eczema, *DC* dendritic cells, *HDM* house dust mites, *SDS* sodium dodecyl sulfate, *TEWL* transepidermal water loss

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