Review

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Mouse Models of Atopic Eczema Critically Evaluated

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Abstract
Atopic eczema (AE) is a chronic relapsing inflammatory skin disorder with increasing prevalence in Western societies. Even though we have made considerable progress in understanding the cellular and molecular nature of cutaneous inflammation, the precise pathomechanisms of AE still remain elusive. Experimental animal models are indispensable tools to study the pathogenic mechanisms and to test novel therapeutic approaches in vivo. For AE a considerable number of mouse models have been proposed and have been used to study specific aspects of the disease, such as genetics, skin barrier defects, immune deviations, bacteria–host interactions or the role of cytokines or chemokines in the inflammatory process. While some models closely resemble human AE, others appear to reflect only specific aspects of the disease. Here we review the currently available mouse models of AE in light of the novel World Allergy Organization classification of eczematous skin diseases and evaluate them according to their clinical, histopathological and immunological findings. The pathogenetic analogies between mice and men will be discussed.

Introduction

Atopic eczema (AE) is a chronically relapsing inflammatory skin disease with a dramatically increasing incidence over the last decades, currently affecting 15–20% of children and 1–3% of adults in Western societies [1, 2]. Clinically AE is characterized by highly pruritic, often excoriated plaques and papules that show a chronic relapsing course, and severely affect the patient in his personal, social and professional life. In addition, AE patients are at increased risk of developing allergic rhinitis or allergic asthma within the atopic march, further decreasing the patient's quality of life [3, 4]. The diagnosis of AE is mostly based on major and minor clinical findings as described by Hanifin and Rajka [5]. Histopathology reveals spongiosis, hyper- and focal parakeratosis in acute lesions, whereas marked epidermal hyperplasia with hyper- and parakeratosis, acanthosis/hypergranulosis and perivascular infiltration of the dermis with lymphocytes, predominantly (CD4) T cells and abundant mast cells are the hallmarks of chronic lesions [6, 7].

A revised nomenclature for allergy has recently been published by the nomenclature review committee of the World Allergy Organization (WAO) [8]. Herein dermatitis is defined as a localized inflammation of the skin. The term eczema – as a subgroup of dermatitis – replaces the provisional term atopic eczema/dermatitis syndrome. Finally, eczema has been further divided into atopic

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Table 1. Animal models of human disease: General consideration

a Requirements for animal models of human disease

Model organism displays cardinal symptoms of the disease
Induction/occurrence of disease phenotype is reproducible
Detailed knowledge of model organism
Sufficient evolutionary homology
Possible transfer of data to man
Model organism has served as model for other diseases (optional)

b Advantages of mice for serving as animal models of human disease (e.g. AE)

Small size, relatively low housing costs
Short generation time, large number of offspring
Availability of inbred (genetically identical) strains
Detailed knowledge about immune system and skin physiology
Availability of genetically altered mice to study gene function (transgenic, conditional knock out, knock in, etc.)
Control of age dependency and of environmental factors (housing, feeding, day-night rhythm, climate, stress, etc.)
Evaluation of novel therapeutic concepts in vivo in high numbers

eczema (AE) and non-atopic eczema (non-AE). AE is characterized by a genetically determined skin barrier defect, an underlying IgE-associated inflammation and lymphocyte infiltration. In non-AE (often referred to as intrinsic AE), which is clinically and histologically indistinguishable from AE, the underlying immune response also shows lymphocyte infiltration, but lacks the involvement of IgE-mediated mechanisms [9].

Several aspects of the pathogenesis of AE have been described, but a complete understanding of the disease has not been achieved so far. Based on a polygenic inheritance [10], striking abnormalities in several components of the immune system have been described, such as elevated levels of total and specific IgE, blood and dermal eosinophilia as well as the infiltration of lesional skin with CD4 cells [7, 9, 11]. In acute lesions, CD4 cells are predominantly of the Th2 type, expressing and secreting IL-4, IL-5 and IL-13, whereas in chronic lesions IFN-γ-producing Th1 cells dominate the immune response [6]. A plethora of additional mechanisms have been implied in the pathogenesis of AE ranging from increased expression of neuropeptides, abnormal responses to vasoactive mediators, altered chemokine expression, to defects in membrane barrier function and lipid metabolism, to name only a few [12]. Even though we have made considerable progress in understanding the multiple facets of the disease, the precise pathomechanism of AE still remains elusive.

Thus, for the analysis of the pathogenic mechanisms and for the development of novel therapeutic approaches, experimental animal models of AE are indispensable tools. A number of different murine models of AE have been reported, some of which display more and others that show fewer aspects of human AE. This review summarizes currently existing mouse models of AE and will discuss the suitability of these models for studies on AE in the context of the current WAO nomenclature. Moreover, AE mouse models will be evaluated with regard to important clinical diagnostic criteria as well as pathogenetic analogies between mice and men.

Mouse Models of AE

Different species including mice, dogs, cats and horses have been reported to develop AE-like skin lesions [13–15]. AE-like symptoms in dogs, cats or horses are diseases present in these domestic companions and are treated as disease states by veterinarians. While a number of analogies in term of clinical manifestation, immunological findings and histology exist between AE in humans and in dogs, cats or horses, these species rarely fulfill the criteria that are required to establish an animal model for human disease (table 1a). Most importantly, in none of these species inbred strains exist that display a stable disease phenotype. In contrast to larger animals, most mouse models of AE fulfill the majority of these criteria. Moreover, mice have a number of additional advantages over other species for serving as animal models of human diseases as outlined in table 1b [16, 17].

The currently reported mouse models of AE can be classified into 4 different, sometimes overlapping categories: (1) mouse models with spontaneous manifestation of AE like skin lesions; (2) genetically engineered mice (transgenic, knockout); (3) AE-like skin lesions induced by protein sensitization, and (4) humanized mouse models of AE generated in mice with severe combined immunodeficiencies, such as the SCID mutant.

Mouse Models with Spontaneous Manifestation of AE-Like Skin Lesions

Mice spontaneously developing disease signs resembling AE have been of particular interest, since this seems to resemble the natural course of the disease in humans. Until today, four different mouse models in which AE-like skin lesions occur spontaneously have been reported.

NC/Nga Mice

The first mouse model reported to spontaneously develop AE-like lesions is the NC/Nga mouse. NC/Nga mice were established in 1957 as an inbred strain from Japanese 'fancy mice' and were the first murine model for AE reported by Matsuda et al. [18] in 1997. In addition to the spontaneous development of AE-like skin lesions, NC/Nga mice spontaneously produce autoantibodies, high levels of C4, show a positive reaction in Coombs test, are highly susceptible to X-ray irradiation and develop glomerulonephritis later in life [19].

NC/Nga mice kept under conventional, non-specified pathogen-free (non-SPF) conditions, develop skin lesions, which parallel human AE in many aspects, including clinical course and signs, histopathology, immunopathology and inheritance. In contrast, NC/Nga mice kept under SPF conditions do not develop skin lesions at all. Interestingly, NC/Nga mice moved from SPF to conventional conditions later in life develop skin lesions later and less severely than mice raised under non-SPF conditions from birth on.

Reciprocally crossing of NC/Nga mice with BALB/c and subsequent backcrossing led to observation of an autosomal recessive mode of inheritance [20]. Linkage disequilibrium analysis identified a major determinant quantitative trait locus on chromosome 9, which was termed *derm1*. This locus corresponds to the human chromosomes 11q22.2–23.3 and 15q21–25 where 7 candidate genes involved in T cell functions (*Thy1, Cd3d, Cd3e, Cd3g, IL-10ra, IL-18* and *Csk*) are located in close proximity [21]. Thus, like human AE, the skin lesions of NC/Nga mice seem to be influenced by genetic as well as environmental factors.

Clinical Signs and Course of Eczema in NC/Nga Mice

The first signs of disease appear in NC/Nga mice kept under conventional conditions at 6–8 weeks, starting with increased scratching, followed by rapid development of erythematous, erosive lesions with edema and hemorrhage on the face, ears, neck and back. The disease peaks at the age of 17 weeks, resulting in lichenificated lesions and blepharitis or ophthalmitis in severe cases. Furthermore, NC/Nga mice display phases of remissions and aggravation similar to human AE, with possible stable remissions after the 6th month of life [22].

Histopathology of Eczema in NC/Nga Mice

NC/Nga mice raised under conventional conditions show no histological aberrations at birth, but before skin lesions become clinically apparent in 6- to 8-week-old mice, degranulated mast cells as well as dermal infiltration with eosinophils and mononuclear cells can already be observed. At the age of 17 weeks, hyperparakeratosis, hyperplasia with elongation of rete ridges and spongiosis are apparent findings. Dermal mast cells, eosinophils and lymphocytes are increased and immunohistochemistry reveals the presence of CD4 T cells and macrophages [18, 23].

Immunopathological Findings in NC/Nga Mice

NC/Nga mice kept under conventional conditions develop elevated total IgE levels at the age of 8–10 weeks correlating with further disease activity, whereas SPF NC/Nga mice do not develop elevated IgE [18]. Further immunopathological findings point towards Th2-biased immune reactions against unknown antigens in NC/Nga mice, as suggested by constitutive tyrosine phosphorylation of Janus kinase 3, leading to an enhanced IL-4 and CD40L-mediated signalling in B cells, resulting in elevated IgE levels [24].

In lesional skin, an overexpression of the Th2 chemokines, TARC and MDC, in basal keratinocytes and dermal dendritic cells as well as increased expression of the chemokine receptor CCR4 were shown, suggesting a predominantly Th2-biased immune reaction in the dermatitis of NC/Nga mice. In addition, a defective Th1 response with low levels of IFN-γ produced by spleen cells and limited suppressive effect of IFN-γ on IgE secretion by NC/Nga B cells were observed. These findings were backed by impaired expression of the IL-12-receptor β chain and defective phosphorylation of the Th1-enhancing transcription factor STAT4 [25]. Interestingly, also STAT6-deficient NC/Nga mice, which lack IgE production and express IFN-γ, IL-12, IL-18 and caspase I in high levels in skin lesions, develop clinically and histopathologically similar skin lesions compared to STAT6-competent NC/Nga mice. Thus, a IgE/Th2/STAT6-independent mechanism for the pathogenesis of NC/Nga mice was proposed, but administration of anti-IL-18 antibodies did not ameliorate the skin lesions [26, 27]. In contrast, the therapeutic effects of IFN-γ, IL-12, as well as IL-18 were reported in another study [28]. Furthermore, subcutaneous injection of TGF-β_1 or dexamethasone led to significant clinical improvement of skin lesions, which histologically corresponded to a reduced number of mast cells and eosinophils within the dermis and was accompanied by a reduction in IgE levels. Furthermore, a reduction in IFN-γ production of splenocytes from TGF-β_1-treated NC/Nga mice was observed and administration of anti-IFN-γ antibody led to a partial reduction in the clinical severity of

the skin lesions [29]. The role of IL-4 and IL-13 in the pathogenesis of skin inflammation was recently addressed by treating NC/Nga with an IL-4/IL-13 receptor inhibitor and kept under conventional conditions. Surprisingly, treated mice displayed an increased eczema severity and IgE levels, suggesting a down-modulatory role for IL-4 and IL-13 in the skin inflammatory immune response [30].

Skin Barrier Abnormalities in NC/Nga Mice

Skin dryness and impaired skin barrier function are hallmarks in the pathogenesis of human AE and also in conventional NC/Nga mice increased transepidermal water loss and abnormal skin conductivity have been observed. Possibly two impairments of ceramide metabolism might cause a predisposition to the development of dermatitis in NC/Nga mice [31]: firstly, an increased activity of ceramidase which breaks ceramide into sphingosine and fatty acids in the skin of conventional NC/Nga mice, and secondly, decreased sphingomyelinase activity in the skin of SPF and conventional NC/Nga mice.

Fur Mite-Induced AE-Like Skin Lesions in NC/Kuj

In a NC substrain (NC/Kuj), infestation with the fur mite *Myocoptes musculinus* under otherwise SPF conditions led to AE-like skin lesions and elevated total IgE. In addition, specific IgE was shown by degranulation of bone marrow-derived mast cells which had been incubated with serum from mite-infested NC/Kuj mice and challenged with fur mite extract. Eradication of fur mites led to resolution of the skin lesions and a reduction in the total IgE titers [32]. No skin changes or IgE elevation were detected in control mice from BALB/c or C57BL/6 background which were infested with *M. musculinus* as well. Thus, the skin manifestations elicited by fur mite in NC/Kuj are a promising model for human AE triggered by house dust mite (HDM) and will deserve further attention.

What Have We Learned from NC/Nga Mice So Far?

AE-like skin lesions in NC/Nga mice are present in a Th2-biased immune setting as well as in skin lesions from STAT6-deficient and Th1-biased NC/Nga mice, suggesting that neither Th2 nor Th1 polarization alone is responsible for the development of AE-like lesions, but that complex dysregulations involving many genes and different proteins such as cytokines, chemokines, proteases, etc., may lead to an AE-like phenotype in NC/Nga mice.

Although abundant in NC/Nga mice, IgE is not a prerequisite for developing dermatitis in NC/Nga, as shown in STAT6$^{-/-}$ NC/Nga strains. Skin lesions in STAT6-deficient NC/Nga mice may thus be regarded as model of non-AE in analogy with the WAO definition of human AE.

In conclusion, the skin lesions developed spontaneously by NC/Nga mice resemble human AE in many aspects, including severe pruritus and a chronic relapsing course of skin lesions, involvement of genetic and environmental factors, skin dryness and impaired barrier function, elevated total and specific IgE levels, histopathology (spongiosis, acanthosis, increased dermal mast cells, inflammatory infiltrate including eosinophils), expression of Th2 cytokines and chemokines, phosphorylation of JAK3 in B-cells and elevated serum IL-18 [22]. NC/Nga mice undoubtedly represent the best characterized mouse model of AE currently available. This is also reflected by its wide use as a test system to evaluate novel therapeutic concepts such as persimmon leaf extracts, NFκB decoy oligodeoxynucleotides, cytokines (e.g. IL-18) or chymase inhibitors [27, 33, 34].

NOA Mice

NOA (Naruto Research Institute Otsuka) mice were initially described as a new hair-deficient mutant and a possible model of allergic dermatitis. NOA mice spontaneously develop total atrichia and pruritic ulcerative dermatitis with dermal mast cell infiltration, as well as high serum IgE [35]. Comprehensive genome analysis with differential display of spleens from NOA mice and corresponding C57BL/6 wild-type mice revealed an overexpression of the chemokine platelet factor-4 and eotaxin, which are known to be strong stimuli for eosinophil attraction in human AE [36]. In addition, linkage analysis identified loci on murine chromosomes 7 and 13, which correspond to consensus areas of linkage to asthma, atopy and elevated serum IgE level on human chromosomes 11q13 and 5q13 [37]. The identification of candidate genes at the consensus area of linkage to asthma and atopy made this mouse model of some interest for elucidation of the genetics of human AE and allergic asthma. However, looking closely NOA mice only partly fulfill the criteria that would allow the clinical diagnosis of AE-like phenotype. While increased dermal mast cells and serum IgE are compatible with AE, primarily ulcerative skin lesions, lack of lymphocytic infiltration and lack of classical histological findings speak against the 'diagnosis' of AE. Taken together, NOA mice may display some aspects of cutaneous inflammation that are also found in AE and thus may serve as useful model to study these specific aspects of cutaneous inflammation.

DS-Nh Mice

DS-Nh mice originated from an inbred strain at Aburai Laboratories in 1976 and were reported as bearing dermatitis associated with *Staphylococcus aureus* in 1997 [38]. DS-Nh mice, kept under conventional, but not under SPF conditions, spontaneously develop itchy erythematous and erosive skin lesions with infiltration of CD4 T cells, eosinophils, mast cells and CD11b+ macrophages. Also total IgE was elevated and correlated with disease severity. Interestingly, skin lesions were colonized with *S. aureus*, which is also an important finding in human AE. Percutaneous sensitization with heat-killed *S. aureus* induced similar skin lesions in DS-Nh mice kept under SPF conditions suggesting a pathogenic role of *S. aureus*. Similar to human AE, transepidermal water loss was elevated with increasing disease activity [39]. Consecutive analysis of the *S. aureus* strains colonizing DS-Nh under conventional conditions shows an abundance of the staphylococcal enterotoxin C (SEC) and additionally, SEC-positive strains were able to survive in skin and draining lymph nodes after intradermal injection [40].

DS-Nh mice show important aspects of AE, but to date no data on specific IgE sensitization are available. Furthermore, total IgE levels as well as transepidermal water loss were increased only after onset of skin lesions, suggesting them to be a secondary epiphenomenon rather than a pathogenetic factor. Therefore, DS-Nh mice seem to be a valuable mouse model for investigation of host–bacteria relationships and the role of *S. aureus* in the development of dermatitis/eczema. The precise subtype of eczema (atopic versus nonatopic) displayed by DS-Nh mice still has to be determined.

Murine Atopic Dermatitis Mice

Murine atopic dermatitis (MAD) mice appear to be another suitable animal model for studying eczema/dermatitis and itch sensation. MAD mice were obtained as a spontaneous mutant from a backcross of 129SV/EV congenic wild types of a corresponding knockout strain into C57BL/6 wild types after the third generation of backcrossing. The phenotype has been stable for >10 generations of breeding and includes skin lesions, itch sensations and increased total plasma IgE levels. In contrast, the corresponding knockout strain that is characterized by the deletion of the two neutrophil granulocyte serine proteases elastase (Ela2) and proteinase 3 (Prtn3) did not show any of the above phenotypes [41]. The penetration of the phenotype was incomplete with 35–40% of the animals showing typical lesions per generation. Significantly more females than males were diseased with a gender ratio of approximately 4:1 (female:male). Eczematous skin lesions in MAD mice occurred only when animals were held under conventional housing conditions (fig. 1). As soon as MAD mice were transferred to SPF conditions, lesions gradually disappeared. Consistent with this finding was the repeated microbiological detection of *Staphylococcus* spp. from skin lesions of MAD mice. A very typical feature of MAD mice was the onset of intense scratching behavior approximately 24 h before macroscopic lesions became apparent. The scratching was confined to certain anatomical regions and mainly involved the cervicodorsal head and neck region (fig. 1) as well as the frontosternal chest region.

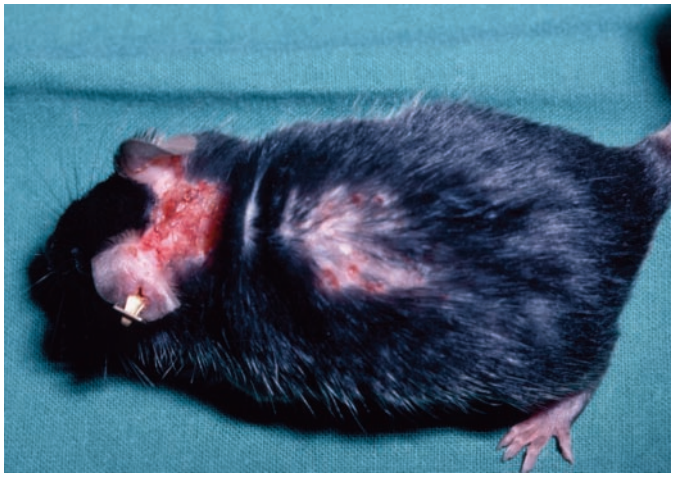

Fig. 1. AE-like lesions in MAD mice. Increased scratching behavior was observed about 24 h before onset of clinically visible lesions.

Morphological analysis of skin biopsies from the cervicodorsal and the dorsal region revealed massive epidermal hyperplasia with parakeratosis, spongiosis and a dense dermal infiltrate (fig. 2b). In non-involved back skin from the same mouse (fig. 2a), as well as in skin from healthy congenic littermates (not shown), no such changes were observed. The immunohistological analysis of leukocyte infiltration revealed positive staining for CD45, CD3, CD4 and occasionally CD8. The CD8-positive T cells were only found in the epidermis, whereas other leukocyte and lymphocyte markers were positive both in the epidermis and dermis (fig. 2c, d). MAD mice displayed increased plasma IgE levels at the time the skin lesions occurred, with a mean of 889 ± 109 ng/ml as compared to healthy congenic controls (69 ± 17 ng/ml; $p < 0.001$). In conclusion, studies on MAD mice suggest this to be a potential new animal model of AE with typical morphological and physiological features of spontaneously arising

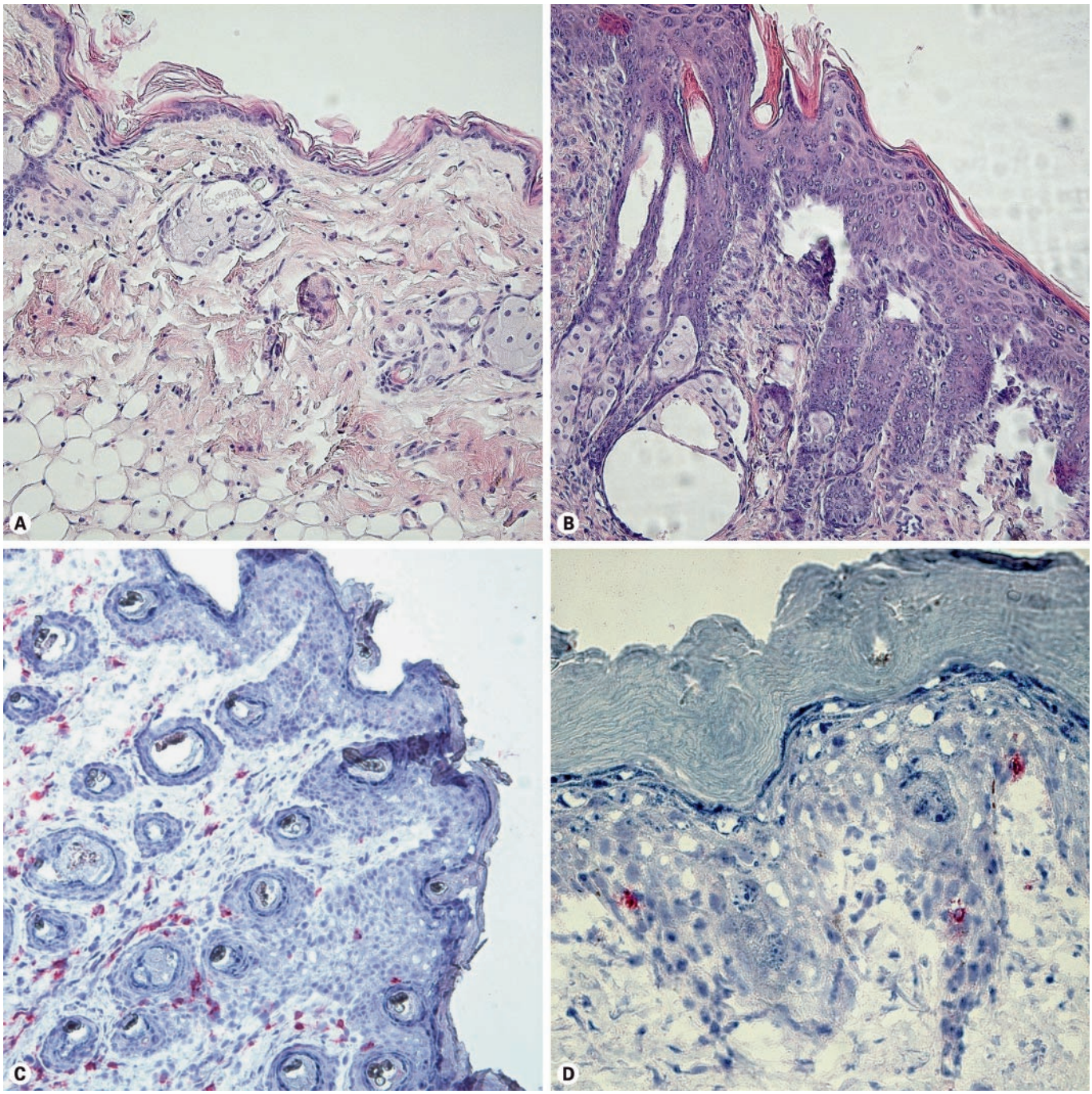

Fig. 2. A HE staining of non-involved skin obtained from MAD mice. **B** HE staining of lesional skin from the same animal, revealing epidermal hyperplasia, acanthosis, spongiosis, parakeratosis and a dense dermal infiltrate. **C** Immunohistochemistry of lesional skin showing a diffuse infiltrate of CD4 cells within the dermis and to a lesser degree in the epidermis. **D** CD8 cells were only found in the epidermis.

AE. Similarly to DS-Nh mice, the precise subtype of eczema displayed has still to be determined.

Genetically Engineered Mice as Models of AE and Chronic Dermatitis

Transgenic and knockout mice are valuable tools in dissecting the specific physiological function of certain genes and proteins and their role in the pathogenesis of disease states. In psoriasis, another chronic inflammatory skin disease, the elucidation of the pathogenetic relevance of interleukins, chemokines, cell surface molecules, etc., has already led to the development of new therapeutic approaches, such as anti-TNF antibodies or anti-CD2 antibodies [42, 43]. Similarly, genetically engineered mice may also help to elucidate the role of individual cytokines in the disease process of AE.

IL-4 Transgenic Mice

In 2001 Chan et al. [44] reported a transgenic (tg) mouse line on a CByB6/BALB/cBy background that expressed IL-4 under the control of the keratinocyte-specific keratin 14 promoter, hence assuring skin-restricted expression of IL-4. These mice spontaneously exhibited chronic itchy skin lesions with scaling and lichenification at 4 months of age. In contrast to NC/Nga mice, K14-IL-4 tg mice also developed dermatitis when kept under SPF conditions [18, 44]. Furthermore, K14-IL-4 tg mice with skin lesions developed staphylococcal pyoderma when kept under conventional conditions, but not under SPF conditions [45]. Histopathology of early lesions showed slight acanthosis, hyperkeratosis, degranulating dermal mast cells and mononuclear cell infiltrate. In chronic lesions, parakeratosis and dermal eosinophils were also observed [44].

Immunopathology of K14-IL-4 tg mice showed increased total serum IgE and IgG1 immunoglobulins – surrogate parameters for Th2 bias – and decreased levels of the Th1 immunoglobulin IgG2a [44, 45]. Furthermore, the CD4/CD8 ratio was elevated to 2.5/1 in skin lesions, and the inflammatory adhesion molecules ICAM-1, VCAM-1, P-selectin and E-selectin were increased on endothelial cells [45]. A treatment with corticosteroid ointment led to significant improvement of the AE-like skin lesions [45].

To conclude, the K14-IL-4 tg mouse model displays pruritus, chronic dermatitis and signs of skin barrier impairment (xerosis and staphylococcal skin infections) as clinical criteria for AE. Moreover, preliminary investigation of T-cell infiltrates suggests a crucial involvement of CD4 cells in the pathogenesis [45]. IL-4 seems to be a precipitating factor for the induction of the eczema in K14-IL-4 tg mice, since these lesions occur as well in mice kept under SPF as under conventional housing conditions. The staphylococcal superinfection of mice under conventional conditions points towards an aggravating role rather than a prerequisite for disease development in this mouse model. In addition, total serum IgE was elevated in most, but not all affected animals and when present, IgE rose with increasing disease activity. Currently, investigations regarding specific IgE are being carried out and, depending on the presence or absence of specific IgE antibodies, conclusions on the role of IL-4 in AE or in non-AE can be derived from this model [45].

Caspase-1 and IL-18 Transgenic Mice

Caspase-1 (CASP1) is an intracellular cysteine protease, involved in processing cytokines (e.g. IL-1β, IL-18) and initiation of apoptotic cell death. Injection of a CASP1-containing plasmid into murine skin lead to localized erythema, granulomatous inflammation and apoptosis after 3 days, lasting up to 3 weeks [46]. In another model, K14-CASP1 tg mice were reported to be healthy at birth but grew slower than non-tg littermates, and after 8 weeks K14-CASP1 tg mice developed a granulomatous and erosive dermatitis which led to mutilating ulcers by week 16 [47]. Histological hallmarks were parakeratosis, infiltration with mononuclear cells and apoptosis. These mice exhibited significantly elevated serum IL-18 levels and slightly elevated IL-1β levels. Analysis of the caspase cascade showed that the downstream enzymes IL-1β, IL-18, CASP3 (an apoptotic executioner) and CAD (an endonuclease) were expressed only in the skin of K14-CASP1 tg mice and not in the skin of wild-type littermates [47].

Elevated IgE production in K14-CASP1 tg mice seemed to be dependent on the downstream cytokine IL-18, as suggested by a significantly lower IgE concentration in K14-CASP1 tg IL-18$^{-/-}$ compared to K14-CASP1 tg IL-18$^{+/-}$ littermate controls [48]. In accordance, IL-18 was shown to induce IgE in BALB/c mice in a CD4 T-cell-, IL-4- and STAT6-dependent manner and also led to an IL-4-dependent Th2 polarization in vitro [48]. Furthermore, IL-18 – when present with IL-3 – was shown to induce the release of IL-4, IL-5 and IL-13. These observation prompted the authors to coin the term 'innate type allergic response' [49]. In subsequent work it was shown that K 14-CASP1 tg as well as K14-IL-18 tg mice develop pruritic erosive dermatitis with acanthosis and increased

dermal mast cells after weeks 8 and 16, respectively [50]. Within this model, STAT6-deficient K14-CASP1 tg mice showed the same degree of skin changes but no IgE production, clearly demonstrating that skin lesions were independent of the presence of IgE. In contrast, IL-18-deficient K14-CASP1 tg mice did not develop eczematous skin lesions, indicating a central role for IL-18 in the development of the skin pathology. Finally, both K14-CASP1 tg and K14-IL-18 tg mice, that were deficient in IL-1α/β, developed dermatitis, however at a later stage in life, suggesting the initiation of dermatitis by IL-18 with acceleration by IL-1 [50].

In conclusion, mice that overexpress CASP1 or IL-18 in the epidermis develop chronic pruritic skin lesions and can serve as a model for chronic eczema. They have helped to elucidate the physiological role of CASP1 and their downstream signals, including IL-1 and IL-18 in chronic inflammation of the skin. Breeding CASP1 or IL-18 tg mice onto appropriate knockout strains has allowed to dissect the involvement of cytokines and demonstrate the lack of involvement of IgE in the pathophysiology of the skin lesions. Since AE is defined as IgE-associated immune reaction of the skin, the K14-CASP1 tg and the K14-IL-18 tg mice may prove useful in the study of non-AE.

IL-31 Transgenic Mice

The phenotype of mice that overexpress the newly discovered Th2 cytokine IL-31 under the control of the elongation factor-1α promoter or the lymphocyte-specific Lck promoter (Lck) was described quite recently [51]. Overexpression of T-cell-dependent IL-31 led to pruritus, scratching behavior and hair loss. Initial skin lesions appear at 4–8 weeks, with a maximum at 6 months of life, histologically showing acanthosis, parakeratosis and dermal infiltration with 'inflammatory cells' as well as mast cells. Subcutaneous injection of IL-31 led to similar skin lesions in BALB/c and C57BL/6 wild-type mice. Total IgE levels were normal. Finally, IL-31 receptor expression was observed in diseased tissue in a model of allergic airway hypersensitivity [51]. It remains to be determined if the newly described IL-31 tg mice represent an additional model for non-IgE-dependent, i.e. non-AE, and thus may contribute a further piece in the puzzle of the various forms of dermatitis and eczema.

Knockout Mouse Models with Dermatitis

RelB-Deficient Mice

RelB is a member of the NFκB transcription factor family, which is predominantly expressed in lymphoid organs and dendritic cells. Besides hematopoietic abnormalities relB-deficient mice also developed spontaneous dermatitis, hyperkeratosis, acanthosis and infiltration with CD4 T cells, eosinophils and to a lesser extent CD8 cells and granulocytes. Furthermore, serum IgE was elevated, and in lesional skin a dramatic increase in IL-4, IL-5, IFN-γ, eotaxin and CCR3 mRNA was detected. In addition, mRNA of TGF-α and IL-1β, proinflammatory cytokines normally secreted by keratinocytes, fibroblasts and macrophages, were increased compared to wild-type mice [52]. Crossing of relB-deficient mice with nur77 tg mice, which lack peripheral T cells, lead to nur77^{TG}/relB$^{-/-}$ mice with strongly reduced epidermal hyperplasia, reduced keratinocyte proliferation and ICAM-1 expression, thus showing that these findings are mainly T-cell-mediated in relB$^{-/-}$ mice [53]. Thus relB-deficient mice showed elevated IgE and some similarities in histopathology, dermal cellular infiltrate and cytokine expression with human AE, whereas an important hallmark – pruritus, as documented by scratching behavior – was not reported. Instead, other severe hematological abnormalities seem to dominate the phenotype, which are rarely reported in AE. The central role of the relB in inflammatory skin processes is evident. Thus relB$^{-/-}$ mice could prove useful as a model for testing specific drugs that interfere with the NFκB pathway, but it has to be kept in mind that such a severely impaired organism will only give first hints for possible actions in wild-type mice or even in humans.

Cathepsin E-Deficient Mice

Mice deficient for the lysosomal aspartic proteinase cathepsin E (Cat E$^{-/-}$) were generated on the C57BL/6 background and were phenotypically normal when raised under SPF conditions [54]. Under conventional conditions these mice developed spontaneously itchy and erosive skin lesions with alopecia. From the lesions *S. aureu*s was cultivated, and histopathology showed epidermal hyperplasia and dermal infiltration with lymphocytes, eosinophils, and macrophages. Total IgE was elevated in Cat E$^{-/-}$ and Cat E$^{+/-}$ mice. Secretion of Th2 cytokines was enhanced in splenocyte cultures from Cat E$^{-/-}$ compared to Cat E$^{+/+}$ mice, while the concentrations of IL-2 and IFN-γ were equal [54]. Furthermore, IL-18 and IL-1β were elevated in Cat E$^{-/-}$ mice. In a consecutive study on AE patients and healthy controls, cathepsin E was shown to be reduced in 70% of patients [54].

The identification of an AE-like phenotype in cathepsin E-deficient mice is a good example in which the observations made in an animal model prompted investigators

to investigate the same pathway in humans, and allowed them to identify a potentially novel player that is dysregulated in pathophysiology of AE.

AE-Like Skin Lesions Induced by Protein Sensitization

Besides the previously mentioned AE models, a number of different approaches have been employed to induce AE-like skin lesions in mice using different protein sensitization protocols. A variety of routes of antigen application (epicutaneous, intradermal, oral/intragastric, intraperitoneal) have been used for sensitization and elicitation. Successful induction of AE-like skin lesions has been reported in different strains (e.g. C3H/HeJ, BALB/c, C57BL/6, NC/Nga) using model allergens such as ovalbumin (OVA), allergen extracts, e.g. house dust extracts, recombinant allergens such as Der p 8, and different food allergens such as peanut or cow's milk. Each of the different protocols was designed to address particular aspects of AE, as detailed below.

AE-Like Skin Lesions Elicited by Epicutaneous OVA Sensitization

Dermatitis with additional asthma-like symptoms can be induced by epicutaneous sensitization with chicken OVA in protocols described by Spergel et al. [55] and Wang et al. [56]. BALB/c, C57BL/6 and subsequently various knockout mice were sensitized by three times repeated application of OVA dissolved in saline, placed in sterile gauze for 1 week on shaved skin at 2-week intervals. Skin lesions in BALB/c mice exhibited significant epidermal and dermal thickening and a mononuclear infiltrate, mainly consisting of αβ- and γδ-TCR CD4 T cells and eosinophils. Elevated serum levels of total and specific IgE and IgG1 as well as increased dermal expression of IL-4, IL-5 and IFN-γ mRNA were observed [55, 57]. In addition, epicutaneously sensitized mice developed asthma-like symptoms after a single exposure to OVA aerosol as documented by bronchial hyperresponsiveness to methacholine, increased bronchial mucus production and eosinophil infiltration [55]. This model shows important aspects of AE, including elevated antigen-specific IgE and AE-like skin lesions. On the other hand, no genetic predisposition, skin barrier dysfunction or pruritus were reported, so that this model may also be regarded as a model of IgE-associated allergic protein contact dermatitis, as described by Hjorth and Roed-Petersen [8, 58].

Making use of the epicutaneous OVA-sensitization model, extensive work was carried out using various null mutants to elucidate the role of cytokines, chemokines and T-cell subpopulations in the pathogenesis of AE [55, 59, 60].

IL-4-deficient BALB/c mice exhibited a Th1-biased skin inflammation with increased numbers of CD45, CD3, CD4 and CD8 cells, and decreased numbers of eosinophils within the inflammatory infiltrate. Further analysis of chemokine mRNA revealed an elevated expression of the Th1 chemokines MIP1α, MIP1β, IP-10 and RANTES, which might lead to the increased dermal T-cell infiltrate in IL-4$^{-/-}$ mice. Also, eotaxin mRNA (an eosinophil-attracting chemokine) was overexpressed only in OVA-sensitized wild-type mice and reduced in IL-4$^{-/-}$ mice, while IL-5 expression was normal [59]. The serological response in IL-4-deficient BALB/c showed decreased IgE and increased IgG2a production, underlining the Th1-biased immune response to epicutaneous OVA sensitization [59].

OVA-sensitized IL-5-deficient mice showed less pronounced epidermal and dermal thickening in comparison to wild-type mice. In addition, IL-5-deficient mice were lacking eosinophils in the otherwise qualitatively unchanged infiltrate consisting of predominantly CD45, CD3ε, CD4 and CD8 cells. No skewing of the serological response was noted [59].

IFN-γ-deficient mice exhibited only slight dermal thickening after OVA sensitization compared to the pronounced increase in wild-type mice, whereas cellular infiltrate and chemokine expression was comparable to sensitized wild-type mice [59].

Cytokine expression was skewed in all three cytokine deletion mutants, leading to enhanced IL-2 and IFN-γ mRNA expression in IL-4$^{-/-}$ mice, increased IL-4 and IFN-γ expression in IL-5$^{-/-}$ mice and elevated IL-4 expression in IFN-γ$^{-/-}$ mice. Interestingly, the elicitation of AE-like skin lesions, inflammatory infiltrate and cytokine expression were unchanged in IgE-deficient mice [59].

Chemokine receptor 3 (CCR3) is expressed on eosinophils, mast cells and Th2 cells and is crucial for the attraction of eosinophils to peripheral tissue. CCR3$^{-/-}$ mice were lacking dermal eosinophil infiltration and major basic protein deposition after epicutaneous sensitization with OVA, whereas mast cell number, mononuclear cells CD3 T cells and expression of IL-4 mRNA were unchanged, and the production of IL-4 and IL-5 by splenocytes was not impaired [61]. Airway hyperresponsiveness and eosinophils in bronchoalveolar lavage fluid were reduced as well, confirming the importance for CCR3 in

the eosinophil attraction and subsequent elicitation of bronchial symptoms [61].

In T cell receptor α-chain-deficient mice neither the dermal infiltrate nor the induction of IL-4 or IgE were observed upon epicutaneous OVA sensitization, thus underlining the crucial role for αβ T cells in the development of AE [60]. In contrast, γδ T cells were not essential for development of skin inflammation, since $\delta^{-/-}$ mice showed no changes in the cellular infiltrate, IL-4 mRNA levels or production of total and specific IgE [60]. In addition, in the same model CD40–CD40 ligand interaction, which is crucial for immunoglobulin class switching and T/B cell interaction, was not necessary for the development of an eosinophil and mononuclear infiltrate. Furthermore, $IgH^{-/-}$ mice lack mature B cells but still develop mononuclear infiltrate and elevated IL-4 mRNA levels. In conclusion, T cells but not B cells are the essential players in the development of AE-like skin lesions upon epicutaneous OVA sensitization [62].

AE-Like Skin Lesions Elicited by Sensitization with HDM Extract or Allergen

In NC/Nga mice kept under SPF conditions, which normally do not develop AE-like symptoms, epicutaneous sensitization with crude HDM extract from *Dermatophagoides farinae* led to dry skin and scratching behavior within 2 weeks. Skin lesions progressed to erosions with hemorrhage and scaling by week 4. No dermatitis was evident in BALB/c mice treated with the same protocol, but in both populations a sensitization with increased total and *D. farinae*-specific IgE and increased IgG1/IgG2a ratio was measured. Mast cell numbers were increased in NC/Nga mice treated with the *D. farinae* extract, but not in BALB/c mice treated with the extract [63]. Since these AE-like lesions appear in mice which are genetically prone to the development of AE like symptoms, they seem to be well suited to serve as a model for AE elicited by epicutaneous sensitization.

In another model the recombinant mite allergen Der p 8 was applied epicutaneously to BALB/c mice, inducing a Th2-biased erosive dermatitis with lichenification and infiltration with CD4 and CD8 cells. Besides morphological changes that go in line with acute dermatitis, nerve fibers were observed in close proximity of mast cells, and immunohistochemistry revealed increased levels of neuropeptides, such as substance P and calcium gene-related peptide. While no data regarding specific IgE sensitization is provided, this model may be of particular relevance to study the neuroimmunological aspects of atopic or non-AE [64].

Murine Model of AE Associated with Food Hypersensitivity to Cow's Milk and Peanut

The high incidence of food hypersensitivities among children with AE prompted Eigenmann et al. [65] to establish a mouse model that could be specifically used to address this aspect of the disease. For that purpose C3H/HeJ mice were sensitized intragastrically to cow's milk or peanut (in this case using cholera toxin as adjuvant) [66]. After repeated oral allergen provocation/boosting, approximately 30–35% of animals developed itchy lichenificated AE-like skin lesions and alopecia with different degrees of involvement ranging from 20 to 90% of the body surface and a chronic relapsing course. Histology revealed spongiosis, epidermal thickening and a dense dermal infiltrate consisting predominantly of CD4 cells, eosinophils and increased numbers of mast cells. Elevated specific IgE levels and blood eosinophilia were noted and intradermal allergen injection resulted in a cutaneous hypersensitivity reaction. The skin lesions resolved under topical corticosteroid treatment or after allergen withdrawal [66].

The skin reaction observed after intragastric sensitization to cow's milk or peanut provoked skin lesions resembling AE triggered or exacerbated by these food allergens and can be used to dissect the underlying immune reactions. In this context, it would be of special interest to know whether these young mice also suffer from gastrointestinal symptoms or malabsorption like affected children, whether the gastrointestinal barrier is also not established fully in newborn mice and why only 30% of syngeneic mice develop dermatitis related to food allergens [67, 68].

Humanized Mouse Models of AE

Severe combined immune deficiency (SCID) mice carry the SCID mutation, a recombinase defect leading to a block in the development of T and B cells, thus allowing reconstitution with xenogenic tissue or blood cells, such as human skin or immune cells, without rejection by the SCID mouse immune system. Hence, to a certain degree SCID mice allow the analysis of human skin and human immune functions in vivo [69].

In SCID mice reconstituted with PBMC of atopic patients sensitized to HDM antigen (Der p 1), the aggravating effect of the superantigen *S. aureus* enterotoxin B (SEB) on the development of cutaneous inflammation was demonstrated in vivo. Concomitant application of HDM extract and SEB elicited a maximal effect on epi-

dermal inflammation and dermal T cell infiltration, whereas SEB alone was less effective and HDM extract lead to dermal T cell infiltration only [70].

Recently, a similar approach was reported in which SCID mice were grafted with skin from healthy human donors and in which the influence of various chemokine receptor ligands on the selective migration of adoptively transferred human Th2 cells was dissected. Shortly, after transplantation of donor skin to SCID mice, Th2 cells derived from skin affected by AE or derived from human PBMC of healthy donors were adoptively transferred, and different chemokine receptor ligands were injected into the skin grafts. Analysis of the T cells within a single cell suspension of the removed graft showed an infiltration with Th2 cells following intradermal injection of CCL22, a Th2 attractant, which could be inhibited by application of antibodies or an antagonist (ESA-2) blocking E-selectin [71]. In a subsequent study the inhibition of Th2 cell migration by CCL4 antagonists was confirmed and in addition, the chemotactic activity of CCL22, CCL2 and CXCL10 on CD3 cells derived from the PBMC of healthy donors was shown. This migration could also be abrogated by administration of the respective antagonists, which underlined the usefulness of this model for the investigation of new therapeutics targeting T cell migration in AE.

Very recently, the adoptive transfer of CD34+ human blood cord cells to newborn Rag1 and common γ chain double knockouts ($Rag1^{-/-}/\gamma_c^{-/-}$) allowed the successful establishment of a functional de novo human immune system within the host, including T cell maturation within the thymus, development of functional lymphoid tissue within the spleen and lymph nodes, formation of dendritic cells and B cells, as well as secretion of immunoglobulins [72]. Even though this concept still requires more detailed analysis, it may represent a novel approach that may prove useful for the generation of an improved humanized mouse model of AE.

To conclude, humanized mouse models such as reconstituted SCID or $RAG2^{-/-}/\gamma_c^{-/-}$ mice are of special interest for the investigation of human AE, since they allow the monitoring of normal and pathological human immune responses in vivo. It is likely that we will hear more about this kind of model in the near future.

Conclusion and Outlook

AE and non-AE are multifactorial diseases characterized by a wide heterogeneity of clinical and immunopathological findings, multiple different trigger factors and an unpredictable course [73]. Mice have contributed a great deal to the understanding of other multifactorial diseases, such as hypertension or diabetes [74, 75]. Given their advantages as laboratory animal (table 1b), mice seem to be the only suitable model organisms available for AE.

In 1997, Matsuoka et al. [63] proposed criteria for mouse models of AE that include clinical findings (dryness, scaling, erythema, erosion and excoriation), pruritus (as documented by scratching behavior), elevation of total and specific IgE and increased mast cells in the upper dermis. On the occasion of the new allergy classification by the WAO, we would like to modify and extend the list of criteria for animal models of AE. We believe that including the WAO criteria for the definition of AE (genetically determined skin barrier defect, IgE-associated immune reaction, lymphocytic dermal infiltrate) will serve to define more precisely valid mouse models of AE. Furthermore, histopathology and immunopathology should display significant similarity to the one observed in human AE. In table 2, relevant findings of the mouse models described above are summarized and listed according to the new comprehensive criteria: the WAO criteria for AE [8]; major clinical findings of AE according to Hanifin and Rajka [5]; histopathology [6], and immunopathology of AE [9]. Using the findings listed in table 2, suitable models may be chosen to address certain pathomechanisms of atopic or non-AE, or to test novel approaches for the treatment of eczema.

It is likely that different disease pathomechanisms lead to the phenotype of AE and non-AE in humans. In this context, the importance of IgE for the AE phenotype is still a controversy. In a recent review of studies regarding the association of 'atopic dermatitis' with specific IgE or positive skin prick testing, a correlation of 45–75% was found in hospital studies and 7–78% in community-based studies [76]. This correlation increased with disease severity and the question was raised whether total and specific IgE elevation is an epiphenomenon rather than part of the pathomechanisms in AE [76]. Also for the differential diagnosis of AE from other skin diseases, exclusion of elevated IgE levels from the diagnostic criteria did not reduce the sensitivity and specificity of Hanifin's and Rajka's criteria [77]. Therefore, a variety of mouse models are needed to investigate the different aspects of this multifactorial disease, especially to illuminate the role of IgE as pathogenetically important or as an epiphenomenon in AE.

In this context it is important to realize that within all the mouse models listed, only in models that use sensitization protocols (e.g. epicutaneous sensitization with OVA,

Table 2. A synopsis of clinical, histopathological and immunopathological findings in mouse models of AE

	NC/Nga[1] [18]	NOA[2] [35]	DS-Nh[3] [39, 40]	MAD[4] [41]	IL-4 tg[5] [44, 45]	CASP1 tg[6] [46, 47]	IL-18 tg[7] [50]	IL-31 tg[8] [51]	RelB$^{-/-}$[9] [53]	CatE$^{-/-}$[10] [54]	OVA sens.[11] [55]	HDM sens.[12] [63]	Der p 8 sens.[13] [64]	Intragastr. prot. sens.[14] [66]	Human-ized models[15] [69–71]
WAO definition [8]															
Genetically determined skin barrier defect	+	n.d.	–	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	–	+ (Nc/Nga)	–	–	–
IgE-associated immune reaction	tIgE ↑ sIgE ↑	tIgE ↑	tIgE ↑	tIgE ↑	tIgE ↑	tIgE ↑	tIgE ↑	–	tIgE ↑	tIgE ↑	tIgE ↑ sIgE ↑	sIgE ↑	n.d.	tIgE ↑ sIgE ↑	tIgE ↑ sIgE ↑
Lymphocytic dermal infiltrate	+	n.d.	+	+	+	n.d.	+	?	+	+	n.d.	+	n.d.	+	+
Clinical symptoms [5]															
Pruritus (documented by scratching behavior)	+	+	+	+	+	+	+	+	n.d.	+	+	+	n.d.	+	n.d.
Chronic (relapsing) course	+	+	+	+	+	+	+	+	+	+	n.d.	n.d.	n.d.	+	n.d.
Eczematous skin lesions/ lichenification	+	alopecia, ulcers	+	+	+	+ ulcers	+	+	+	+	+	+	+	+	+
Histopathology [6]															
Spongiosis, acanthosis, hyper-/parakeratosis	+	+	+	+	+	n.d.	+	+	+	+	+	+	+	+	+
Dermal infiltration: Predominantly CD4 cells, eosinophils, mast cells	+	n.d. dermal MC ↑	+	+	+	n.d.	+	+	+	+	+	+	+	+	+
Immune deviations [9]															
Th 1/2 dysbalance	+	n.d.	+	n.d.	+	+ (spleen)	+ (spleen)	n.d.	+	+ (spleen)	IL-4, IL-5, IFN-γ ↑	n.d.	+	+	+
Other immune deviations	–	n.d.	n.d.	n.d.	n.d.	IL-1β ↑, IL-18 ↑	n.d.	n.d.	DC ↓, multiple	n.d.	n.d.	n.d.	n.d.	–	n.d.

+ = Criteria fulfilled; – = criteria not fulfilled; n.d. = not determined/documented; BIR = bronchial inflammatory response; BHR = bronchial hyperreactivity; inflam. = inflammation/ inflammatory; sens. = sensitization.

1 IgE-independent eczema[16]; NC/Kuj infested with fur mite.
2 No clear AE-like skin phenotype.
3 *S. aureus*.
4 *Staphylococcus* spp.
5 Pyoderma with *S. aureus/P. aeruginosa*.
6 Mutilating ulcers, apoptosis ↑ IgE-independent eczema[16]
7 IgE-independent eczema[16].
8 Inflam. skin infiltrate not specified, normal IgE.
9 Multi-organ inflam., impaired development of lymphoid organs.
10 *S. aureus*, sIL-18 ↑, sIL-1β ↑.
11 Bronch. inflam./BHR; IgE-independent eczema[17].
12 HDM sens. in NC/Nga.
13 Cutaneous neuropeptides ↑.
14 Cutaneous type-I hypersensitivity to cow's milk.
15 Human skin/immune cells in immunocompromised mouse in vivo.
16 IgE-independent eczema as demonstrated by the occurrence of eczematous lesions in STAT6$^{-/-}$ mice.
17 IgE-independent eczema as demonstrated by the occurrence of eczematous lesions in IgE$^{-/-}$ mice.

HDM extract or intragastric protein sensitization) was an elevation of specific IgE reported. Strictly speaking, only these models may be regarded as suitable models for AE according to the WAO criteria. In the majority of the other models only increased total IgE is reported and we have no information whether this is directed against environmental allergens or just polyclonal IgE elevation as an epiphenomenon of the cutaneous inflammation. While in humans we have ample evidence for a crucial role of specific IgE in the pathogenesis of AE, the precise contribution of IgE to the development of eczematous skin lesions in mice is not clear. Human skin dendritic cells express the low- (CD23) and the high-affinity receptor for IgE (FcεRI, in its heterotrimeric form ($\alpha\gamma\gamma$)), and allergen binding via specific IgE facilitates allergen uptake, processing and presentation [78–80]. In contrast, dendritic cells in mouse skin express neither FcεRI nor CD23 [81, 82], suggesting that if specific IgE is involved, it must act via different mechanisms than in man. Genetically engineered mice that express IgE receptors also on dendritic cells may help to elucidate this aspect of the disease. While in the majority of the models described the significance of increased total IgE remains unclear, other models (e.g. NC/Nga, CASP1$^{-/-}$, OVA sensitization model) clearly demonstrated that development of eczematous skin lesions was also possible in the absence of IgE, i.e. when

mice were bred on a strain background that was unable to develop IgE immune responses such as IgE or STAT6 null mutants. These mouse models may prove particularly useful for the studies of IgE-independent non-AE.

In an overall evaluation, Nc/Nga mice are with no doubt the model which resembles human AE more than any other available mouse model. The remaining models seem to be particularly useful to address specific aspects of the disease. Genetically engineered mice have already proven to be of high value for understanding the in vivo effects of certain cytokines or chemokines in the pathogenesis of the disease, and more questions are likely to be answered with these approaches. The specific role of colonization with *S. aureus* is an almost obligatory finding in AE [83]. In this context, DS-Nh mice and MAD mice might prove to be valuable tools in dissecting the host–bacteria relation and the mechanisms leading to aggravation or even initiation of AE by microbial factors, such as superantigens [40, 41, 84] or staphylococcal cell wall components such as peptidoglycan or lipoteichoic acid [85]. Sensitization to environmental factors or food allergens is another important aspect of AE, and these findings were clearly supported by mouse models with sensitization to fur mites, HDM extract, the recombinant HDM allergen Der p 8 and food allergens [32, 63, 64, 66]. Interesting applications, such as further dissection of the sensitization process in vivo, breaking of tolerance, as well as elucidation of the mechanisms in specific immune therapy might be approached.

In conclusion, a large number of mouse models of AE have been described so far, some of which fulfill all or most of the relevant criteria to serve as a model for AE, while others only represent certain aspects of the disease. We now await the application of these in vivo systems for the analysis of the complex interactions of the skin and immune systems in AE and description of currently unknown pathomechanisms. Last but not least, these models are indispensable tools to evaluate the efficacy and safety of novel approaches in the treatment of eczematous skin diseases. Substantial contribution of mouse models to foster our understanding and improve therapy for AE and non-AE can be expected. For correct interpretation of findings in mouse models of AE, we suggest the integration and evaluation of the clinical, histopathological and immunological criteria given in table 2. In this way we can optimize what we can learn from these models and may come to the same conclusion as Baruj Benacerraf who once said 'mice never lied to us'.

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