

Skin Inflammation Models in Animals

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Synonyms

Mouse model; Skin inflammation

Definition

Inflammatory skin diseases are caused by dysregulation of tissue homeostasis due to external or internal trigger factors. Animal models are being used to study the underlying pathomechanisms.

Animal Models for Inflammatory Skin Disease

Skin diseases can be classified according to coding in the International Statistical Classification of Diseases and Related Health Problems (ICD) published by the WHO in its latest version in 2010 (ICD-10 Chapter XII, L00-L99, www.who.int/classifications/icd/). They have many different causes and are associated with a disruption of tissue homeostasis. Tissue homeostasis is an active process that is tightly regulated by genetic and epigenetic programs and physiological processes. A tightly balanced interaction of the body surfaces such as the skin, gut, and lung with their specific – locally and individually different – microbiota is an important element of homeostasis. The skin microbiome comprises a huge community of commensal microorganisms which are not only found on the skin but also in hair follicles, sweat glands, and sebaceous glands. Some of the skin resident microorganisms are beneficial for skin function but are also potential pathogens such as *S. aureus* or *P. acnes*. These microorganisms are kept in check, for example, by the acidic skin pH and by natural antibiotics, families of antimicrobial peptides (AMP), produced in the skin. Abnormal AMP production is an important factor contributing to inflammatory skin diseases such as atopic dermatitis and psoriasis (Grice and Segre 2011; Gallo and Hooper 2012).

Any disturbance of the steady state is sensed by tissues by different means and results in processes that aim at the restoration of homeostasis. The surface area of the human skin comprises about 2 m². It is an important mechanical and immunological barrier to the outer world and is constantly exposed to the environment. Therefore, it has to deal with all kinds of assaults such as infectious agents, environmental noxae, chemicals, or UV irradiation. Disturbed skin homeostasis often results in breakdown of barrier function and inflammation, and a lack of restoration promotes the development of often chronic inflammatory skin diseases including infectious diseases and autoinflammatory and autoimmune diseases. Genetic defects such as null mutations of the gene for filaggrin that critically regulates skin barrier function also result in or predispose to inflammatory skin diseases (De Benedetto et al. 2012; Irvine et al. 2011). Prototypic sensors for infection but also for sterile inflammatory processes are the receptors of the innate immune system. These include the cell-associated Toll-like receptors (TLRs), cytosolic

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Table 1 Types of animal models for inflammatory skin diseases

Mouse model	Disease occurrence
Wild-type mouse strains	Induced
Mutant mouse strains	Spontaneous
Genetically engineered mouse models	Disease occurrence
(Inducible) knockout/transgenic mouse strains	Spontaneous/induced
(Inducible) cell type-depleting transgenic mouse strains	Spontaneous/induced

NOD-like receptors (NLRs), and RIG-I-like receptors (RLRs) but also soluble receptors in the extracellular space such as complement components, pentraxins, collectins, and ficolins (Bottazzi et al. 2010).

The common theme in inflammatory diseases of the skin and other tissues seems to be the disturbance of tissue homeostasis and barrier function leading to sterile inflammation that may be amplified by altered microbiota-tissue interaction.

This overview focuses on mouse models of inflammatory skin diseases. Inbred mouse strains have the advantage of defined and well-characterized genetics, and they allow studying the highly complex in vivo processes that are often not or only partially reproducible in in vitro systems, in part due to significant gaps of knowledge in mechanistic understanding. These gaps of knowledge can be closed by in vivo studies. Constitutive or inducible gene knockout/knockin and transgenic gene (over)expression methods as well as depletion of specific cell types with monoclonal antibodies or by modern genetic approaches and transfer of cells from wild-type, transgenic, or knockout mice enable the dissection of the molecular and cellular pathomechanisms and to design disease models. Therefore, mouse models are valuable tools for basic and preclinical research serving the understanding of human diseases, with all known limitations. They not only help to identify new drug targets and to develop new treatments, but they are also important to establish mechanistically defined endpoints which can be implemented for the development of in vitro assays for diagnostics and immunotoxicology. This should allow a stepwise reduction and eventually replacement of animal-based test systems by defined in vitro, in silico, and in chemico test systems that faithfully reproduce crucial steps of the disease pathogenesis.

Several spontaneous, inducible, transgenic, and knockout mouse models for inflammatory skin diseases exist (Table 1). A useful technology is the flanking of genes of interest with loxP sites, recognition sites for the adenoviral CreDNA recombinase. Cre recombinase transgenic mice are then mated with a strain expressing the loxP-flanked (floxed) gene. When Cre is expressed, the floxed gene is eliminated by a recombination process. Cre is often expressed under the control of a cell type-specific promoter and can even be made inducible. This allows, for example, a targeted and timed gene knockout. A common technique is the fusion of the Cre gene to a mutant estrogen receptor ligand binding domain that requires tamoxifen for activation. Cre is then only activated when mice receive tamoxifen (Belizário et al. 2010).

Some examples for each of the different mouse model categories will be given in the following chapters that illustrate the basic principles of the different models and the types of studies conducted.

Dysregulation of Epidermal Homeostasis Induces Skin Inflammation in Animal Models

Skin homeostasis is regulated by many factors. Among those, the transcription factor NF- κ B plays a very important role. NF- κ B is involved in different signaling pathways including those that regulate inflammation and apoptosis (Hoffmann and Baltimore 2006). NF- κ B signaling must be tightly regulated. Therefore, NF- κ B activation is negatively regulated by the inhibitory protein I κ B. Upon stimulation of

receptors such as TLRs, I κ B is inactivated, and NF- κ B translocates into the nucleus to bind DNA binding sites in promoter regions of NF- κ B-regulated genes enabling their transcription. The I κ B kinase beta (IKK β or IKK2) is part of the so-called canonical NF- κ B signaling pathway. IKK β phosphorylates I κ B which results in its degradation by the proteasome. Mice with a deletion of the negative regulator for NF- κ B, I κ B α , show strongly increased NF- κ B activation and strong generalized inflammation by day 3 after birth. This includes skin inflammation characterized by erythematous thickening and scaling. The animals die by day 7 or 8. Keratinocyte-specific I κ B α -knockout (keratin 5 (K5)-Cre2) mice exhibit acanthosis and hyperkeratosis but fail to develop spontaneous epidermal inflammation. The skin disease improves progressively. Inflammation only develops when I κ B α is also deleted in T cells. This underlines the role of T cells for initiation and maintenance of the inflammatory skin phenotype observed in the complete knockout mice (Rebholz et al. 2007).

Mice lacking IKK β in keratinocytes (K5-Cre) develop inflammatory disease including spontaneous skin inflammation with infiltrating macrophages and other CD45⁺ immune cells. The chronic inflammation is T- and B-cell independent and resembles interface dermatitis with epidermal basal cell injury, increased inflammatory cytokine production, and upregulation of genes typically associated with inflammation (Page et al. 2010).

Human polymorphisms in the gene for the ubiquitin-editing enzyme A20 (TNFAIP3) are associated with inflammatory disorders such as psoriasis. A20 negatively regulates NF- κ B signaling and is involved in skin homeostasis and epidermal appendage development. Mice with a keratinocyte-specific A20 deletion (K14-Cre) develop keratinocyte hyperplasia but no spontaneous inflammation or scaling of the skin. Ectodermal appendages are abnormal: the mice have thinner, more fragile, and curly hair, longer nails, and sebocyte hyperplasia. The A20-deficient mice have a phenotype that copies the phenotype of transgenic mice overexpressing either the TNF family member ectodysplasin A (EDA) or the TNF family receptor ectodysplasin A receptor A1 (EDAR) which regulates NF- κ B levels. Thus, overactivation of the EDA pathway or lack of negative regulating of EDA-induced NF- κ B levels severely impacts skin homeostasis (Lippens et al. 2011).

Animal Models for Autoimmune Blistering Diseases

Autoantibody production to protein components of cellular adhesion complexes in the epidermis is associated with the loss of cell-cell adhesion between keratinocytes or loss of keratinocyte basement membrane adhesion and formation of skin blisters in locations that are characteristic for the target autoantigen and the disease. Typical diseases are pemphigus vulgaris (PV), epidermolysis bullosa acquisita (EBA), and bullous pemphigoid (BP). Two principal models exist: *Passive mouse models* are established by the injection of autoantibodies from patients or other species. *Active mouse models* make use of autoantigens injected into mice (Amagai 2008; Leighty et al. 2007; Sitaru 2007; Ganeshan et al. 2010).

In PV desmogleins (Dsg) 1 and 3, constituents of desmosomes that mediate cell-cell adhesion of keratinocytes, are the target autoantigens. Autoantibody production leads to acantholysis, the loss of intercellular keratinocyte adhesion. Passive models using injection of antibodies to Dsg failed to induce spontaneous blistering. A more successful approach makes use of Dsg3-deficient mice immunized with Dsg3 (Aoki-Ota et al. 2004). This leads to the induction of Dsg3-specific B and T cells which induce pemphigoid-like blistering disease when transferred into Rag-2-deficient recipient mice which lack B and T cells. Dsg3-deficient mice do not develop B- and T-cell tolerance to Dsg3 and can therefore be efficiently immunized. The transferred B and T cells then are activated by Dsg3 in the Rag-2 recipient, and the B cells produce pathogenic anti-Dsg3 IgG over a sustained period of time.

Collagen VII, a main constituent of anchoring fibrils of hemidesmosomes, adhesive complexes connecting epidermis and dermis, is the autoantigen in EBA. Autoantibodies to collagen VII and complement component C3 can be found deposited in the skin and are involved in the separation of the dermal-epidermal junction and subepidermal blister formation. The passive EBA mouse model makes use of anti-collagen VII antibodies (IgG) generated by immunization of rabbits with mouse or human collagen VII. Repeated injection of the purified IgG into susceptible mouse strains leads to blister formation but does not recapitulate other aspects of EBA. The injection of patient autoantibodies is of limited success. The active mouse model of EBA is based on the repeated subcutaneous injection of recombinant mouse collagen VII with adjuvants. This induces autoantibodies to collagen VII and blistering disease in susceptible mouse strains.

In BP the main autoantigens are collagen XVII (BP180) and BP230. They are both constituents of hemidesmosomes. Also here passive and active mouse models have been established. In the passive model blister formation is not induced spontaneously by injection of patient antibodies but only after shear stress applied to the skin. Injection of rabbit antibodies specific for collagen XVII induces subepidermal blister formation in mice. Recently, active models have been established that again use the injection of recombinant collagen XVII or fragments thereof. Repeated autoantigen injections can break tolerance and induce BP (Hirose et al. 2011).

The passive BP model is a prime example of the use of mouse models to dissect pathomechanisms at a cellular and molecular level. Thus, a series of publications used mast cell-deficient mice or depletion of neutrophils or macrophages, knockout mice lacking Fc γ RIII, T/B-cell-deficient mice, or knockout mice lacking the complement component C5, the C5a receptor or the neutrophil effector molecules gelatinase B or elastase (Leighty et al. 2007; Heimbach et al. 2011). The results demonstrated an important role for macrophages and mast cells and of complement C5 in the recruitment of neutrophils and mast cell activation, as well as a role for Fc γ RIII, gelatinase, and elastase in neutrophil activation and effector function. A further study with humanized BP180 mice demonstrated a role for autoantibody-mediated activation of innate immune players such as complement, mast cells, and neutrophils which required the presence of the Fc portion of IgG. A recent study supported the role of neutrophils as important innate effector cells in BP using a novel active mouse model (Oswald et al. 2012). In this model mice were pre-immunized against rabbit IgG and then repeatedly injected with murine collagen XVII-specific rabbit IgG leading to the formation of immune complexes. Deposition of C3 and IgG at the dermoepidermal junction was observed. The mice developed sustained subepidermal blistering disease resembling human BP. Here, a role for Fc γ R-dependent immune complex-triggered neutrophil activation and respiratory burst was demonstrated. Neutrophil depletion partially inhibited blister formation.

An elegant approach to study blistering disease is the generation of the so-called humanized mice (Nishie et al. 2007, 2009; Ujiie et al. 2010). This is achieved, for example, by expression of human collagen XVII under a keratinocyte-specific promoter in mice. Transplantation of the skin from transgenic mice onto wild-type mice results in autoantibody production, blister formation, and eventually rejection of the skin graft. Injection of patient antibodies into collagen XVII-humanized mice induces blister formation indicating that human collagen is efficiently targeted by the autoantibodies. Moreover, newborn human collagen XVII transgenic mice develop disease following transfer of maternal anti-collagen XVII antibodies (Nishie et al. 2009). Immunization of wild-type mice to human collagen XVII via skin transplants from the humanized mice followed by transfer of their spleen cells into Rag-2-deficient human collagen XVII transgenic mice results in sustained autoantibody production and disease.

Psoriasis

Psoriasis is a T-cell-dependent inflammatory autoimmune skin disease. The culprit autoantigens are not yet known (Perera et al. 2012). The pathogenesis depends on IFN- γ secreting T helper (Th)1 cells, but more recently a crucial contribution by IL-17 and/or IL-22 secreting CD4⁺ Th cells (Th17, Th22 cells) has been demonstrated. For the differentiation of Th1 and Th17 cells, the cytokines TNF- α , IL-12, and IL-23, respectively, which are produced by DCs and macrophages are very important. The current rather successful immunotherapy is based on injection of a monoclonal antibody that binds and neutralizes the p40 subunit that is common to these heterodimeric cytokines. In vivo models of psoriasis also use mutant and genetically engineered mice (Danilenko 2008; Jean and Pouliot 2010). All of these mouse models only partially recapitulate the human condition. Two common spontaneous mouse models are the flaky skin mouse and the SHARPIN mouse. The flaky skin mouse develops focal parakeratosis which, in sharp contrast to human psoriasis, is however T-cell independent. The SHARPIN mouse also develops a T-cell-dependent focal parakeratosis, but other than the Th1-/Th17-mediated human disease, this phenotype is Th2 mediated. A series of transgenic mouse models have been established that use, for example, overexpression of adhesion molecules (CD18) and cytokines (IL-12/IL-23p40, TGF- β) often targeted by a keratinocyte-specific promoter to epidermal keratinocytes. Also in these models only some aspects of psoriasis are reproduced.

KC-Tie2 mice express the angiopoietin receptor 2 (Tie2) as a transgene in keratinocytes (KC) (Ward et al. 2011). These mice develop psoriasiform skin disease with infiltrating abundant macrophages in lesional skin as observed in humans. In this model macrophages were depleted by injection of liposomes containing clodronate. Liposome uptake by macrophages and clodronate release into the cell kills them. This treatment reversed acanthosis and dermal angiogenesis and resulted in normalized T-cell numbers and reduction of crucial pathogenesis driving cytokines such as IL-6 and IL-23. These findings emphasize the importance of macrophages in inflammatory skin disease.

Atopic Dermatitis

Atopic dermatitis (AD) collectively describes inflammatory hypersensitivity reactions elicited by usually harmless substances that come in contact with the skin (Boguniewicz and Leung 2011). Several mouse models are being used to study the pathomechanisms of AD (Jin et al. 2009; Tanaka et al. 2012). Inbred *Nc/Nga* mice represent a spontaneous model for human atopic dermatitis (AD). They harbor a mutation on chromosome 9 that under conventional housing conditions is associated with the spontaneous development of skin barrier defects and subsequently typical signs of AD such as hyperparakeratosis, hyperplasia, and spongiosis. Another interesting spontaneous model is the *DS-Nh mouse*. These mice also develop AD under conventional housing conditions and, most interestingly, show heavy colonization of lesional skin with *S. aureus* found in human AD as one of the most important exacerbating factors. *Cby.Aly-aly* mice also develop spontaneous dermatitis with *S. aureus* infection of lesional skin.

Other approaches to study AD use the transgenic overexpression of factors associated with the immune response in the disease. One of these factors is thymic stromal lymphopoietin (TSLP) which is highly expressed in keratinocytes of lesional skin of AD patients. TSLP promotes Th2 responses by acting on DCs. TSLP transgenic mice which overexpress TSLP under the K5 promoter specifically in keratinocytes have been generated: These mice spontaneously develop a Th2-mediated inflammatory AD-like skin disease (Yoo et al. 2005). Among various other factors that upon transgenic overexpression in the epidermis lead to AD-like symptoms in mice are T-cell cytokines such as IL-4 or IL-31.

One of the most important findings in recent years was the association of AD with loss of function mutations of the protein filaggrin (FLG), a component of the outer layers of the epidermis (Irvine et al. 2011). FLG regulates hydration, surface pH, and terminal keratinocyte differentiation. The barrier function of the skin is significantly reduced in FLG-deficient spontaneous mouse mutants (Fallon et al. 2009). Homozygous flaky tail (*ft*) mice develop a spontaneous AD-like skin disease already at 3 days of age that is observed as flaking tail skin. It was recently discovered that these mice have a null mutation in the *flg* gene. Allergen application to the skin of these mice is sufficient to induce a strong inflammatory infiltrate.

Atopic dermatitis-like disease can be induced by removal of the upper skin layers by tape-stripping of shaved mouse skin and subsequent epicutaneous challenge with protein antigens such as chicken ovalbumin (OVA) or house dust mite allergen. In wild-type mice it was demonstrated that repeated application of the house dust mite allergen Der f can lead to atopy-like symptoms (Hennino et al. 2007). Interestingly, evidence was provided that not only CD4⁺ T cells are involved in the pathogenesis but that CD8⁺ T cells are participating. The observed early CD8⁺ T-cell infiltration suggested a pioneering role for CD8⁺ T cells as early initiators of the inflammatory response and a later dominance of CD4⁺ T cells (Hennino et al. 2011). At early time points of patch test reactions, CD8⁺ T-cell infiltration was also observed in the human skin. In this model it was even possible to establish a successful sublingual immunotherapy (SLIT) protocol (Vanbervliet et al. 2012).

Contact Dermatitis

Irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD) are inflammatory skin diseases that are triggered by chemicals (Martin et al. 2011; Vocanson et al. 2009). Eczematous skin reactions are the result. While ICD is mediated by the toxic irritant effects of chemicals without involvement of the adaptive immune system, i.e., B and T cells, ACD is initiated by chemical-induced activation of the innate immune system followed by activation of chemical-specific T cells. The T cells are of the Th1/Tc1 and Th17/Tc17 type and are the main effector cells in ACD. They cause spongiosis in the skin due to cytotoxic activity. About 4,000 organic chemicals and metal ions such as nickel and cobalt are known as contact sensitizers. The mouse model for ICD and ACD is the contact hypersensitivity (CHS) model. In this model many aspects of the immune response to allergenic chemicals are analyzed that are often paralleled by adverse immune responses to drugs (Martin 2012). In the CHS protocol a single epicutaneous application of the contact sensitizer onto the shaved abdominal mouse skin leads to sensitization by activation of skin cells due to the chemical-induced innate inflammatory response. Activated dendritic cells (DCs) migrate to the skin draining lymph nodes presenting contact sensitizers in the context of MHC molecules to T cells. The contact sensitizer-specific T cells are then primed and expand. Circulating effector T cells are recruited into the inflamed skin where they exert effector functions including cytotoxicity and cytokine production after a second application of the same contact sensitizer to the ear skin, for example, on day 5 after sensitization. Within 24–48 h the ear skin shows an edematous swelling reaction which is measured using an engineer's micrometer. This is the classic mouse ear swelling test (MEST).

Metal ions such as nickel and cobalt cannot induce CHS by themselves. The reason for that is their inability to bind and activate mouse Toll-like receptor 4 (TLR4), an essential trigger for skin inflammation in CHS. They readily do that in humans since the binding sites for these metal ions are only present in human but absent in mouse TLR4. This problem can be circumvented by mixing nickel or cobalt ions with a TLR4-activating agent, the natural TLR4 ligand lipopolysaccharide (LPS) from gram-negative bacteria which in that case acts as a potent adjuvant. The case of these metal ions is a good example for the

limitations of animal models, here due to species-specific differences. On the other hand, *in vitro* assays for DC activation with organic chemical allergens such as 2,4,6-trinitrochlorobenzene (TNCB) only yield partial activation of human and mouse DCs. This is due to the fact that signals from the extracellular matrix of the skin, i.e., degradation of hyaluronic acid to low molecular weight fragments that trigger TLR2 and TLR4 and therefore enable full DC activation, resulting especially activation of NF- κ B signaling and pro-inflammatory cytokine production, are missing *in vitro* (see also below). This example impressively demonstrates the limitations of *in vitro* models. In conclusion, it is important to understand in detail molecular and cellular mechanisms in order to define the specific limitations of each *in vivo* and *in vitro* model. Here, *in vitro* and *in vivo* studies complement each other.

Weak contact allergens such as fragrances which cause many problems with human ACD can now also be tested in the mouse model. It has been recognized that CHS does not occur unless these weak contact allergens are applied repeatedly, e.g., once daily on three consecutive days for sensitization in mice that have been pretreated with antibodies against CD4. The reason for that is the presence of CD4 expressing regulatory cell populations such as conventional regulatory cells and NKT cells which actively prevent CHS responses to weak contact allergens and can be considered as a brake for immune responses. Strong contact allergens induce enough inflammation to overcome the action of these regulatory cells and release the brake.

The CHS model is also used to study the induction of tolerance to contact allergens. In man, repeated exposure to weak contact allergens such as fragrances may induce T-cell tolerance instead of ACD. In the CHS model repeated application of very low doses of strong contact sensitizers that are 100–1000-fold lower than the dose used for sensitization leads to the so-called low zone tolerance (LZT). In this model the role of regulatory T cells and DCs in the induction of contact sensitizer-specific tolerance can be studied in great detail. Here, depletion or adoptive transfer of specific cell types is used to study the role of these cell types and their interaction with other cell types. Mice lacking cytokine receptors or other molecules involved in LZT are used to identify important molecular players.

The constitutive or inducible deletion of specific cell types is nowadays achieved by generating transgenic mice which express the diphtheria toxin A (DTA) subunit which is toxic for the respective cell type and leads to constitutive depletion or mice expressing a human or rat diphtheria toxin receptor (DTR) under the control of a cell type-specific locus. These DTR are much more sensitive than the mouse DTR and therefore allow killing the DTR⁺ cell type by injection of diphtheria toxin (DT) at the time point of choice. Using this technique it was shown in the CHS model that regulatory T-cell depletion leads to stronger and prolonged CHS responses (Lehtimäki et al. 2012) or that the absence or depletion of mast cells almost completely abrogated CHS (Dudeck et al. 2011). A nice strategy in the design of targeting constructs for such vectors is the use of constructs with an internal ribosomal entry site (IRES) that allows expression of two transgenes simultaneously from the same promoter. A common strategy is using a fluorochrome tag such as green fluorescent protein as the second transgene. This allows to easily identify, for example, the DTR-positive cells since they have green fluorescence. This technique is ideal to monitor the cell population expressing the transgene of interest *in vivo*, for example, by confocal microscopy or *in vitro* by immunofluorescence or flow cytometry.

Chronic application of some experimental contact sensitizers leads to a Th2-type immune response that is often described as a model for chronic contact dermatitis but is also considered to represent an inducible AD-like mouse model.

Similar to the methods described for the BP model, the pathomechanisms of CHS can also be studied using monoclonal antibody depletion, cell transfer, and transgenic and knockout mice. By using knockout mice that lack different receptors associated with innate inflammatory responses, it was demonstrated that contact sensitizers trigger an innate immune response that is very similar to the one triggered by pathogens (Martin et al. 2011). It was shown that organic chemicals such as the strong contact sensitizer TNCB

induce rapid production of reactive oxygen species (ROS) that initiate the degradation of hyaluronic acid (HA), a component of the extracellular matrix of the skin (Esser et al. 2012). Moreover, ROS activate and amplify signaling pathways that promote inflammation and upregulate hyaluronidases which then further degrade HA. Low molecular weight HA fragments then trigger TLR2 and TLR4 activation leading to NF- κ B signaling and production of pro-inflammatory cytokines such as IL-6, IL-12, TNF- α , and immature pro-IL-1 β and pro-IL-18

Furthermore, cell stress and damage as caused by contact sensitizer leads to the release of ATP. Extracellular ATP is a danger signal that is perceived by purinergic receptors on cells. The P2X7 receptor (P2X7R) binds ATP and contributes to the activation of the NLRP3 inflammasome, a cytosolic protein complex consisting of the NLR NLRP3, and the adaptor protein ASC. The inflammasome activates caspase-1 which then cleaves immature pro-IL-1 β and pro-IL-18 to their mature and secreted forms. These cytokines, especially IL-1 β , are crucial mediators of skin inflammation in CHS. This very detailed picture of the sterile skin inflammation caused by contact sensitizers was revealed by studies in knockout mice. Mice lacking TLR2 and TLR4 or NLRP3 or ASC or P2X7R or IL-1 receptor are all resistant to sensitization and CHS induction. By adoptive transfer of contact sensitizer-presenting and T-cell-activating DCs from wild-type or knockout mice into wild-type or knockout recipient mice to it was then also shown that it is sufficient for sensitization that these TLRs, P2X7R, and NLRP3 or ASC are functional in DCs. Interference with the identified pathways was shown to prevent sensitization or even elicitation of CHS. These data will now lead to clinical studies and hopefully to the development of causative treatment strategies for ACD.

Summary

Mouse models have proven to be very useful to gain insights into cellular and molecular pathomechanisms of human disease in a complex in vivo setting. The limitations of each model such as species-specific differences have to be carefully defined as is the case for in vitro models. In vivo and in vitro models therefore complement each other and profit from clinical studies. Altogether the data generated can be used for the development of new treatment strategies by the identification of drug targets and for the improvement of existing and development of new in vitro assays for diagnostics and immunotoxicology.

Cross-References

- ▶ [Allergic Disorders](#)
- ▶ [Atopic Dermatitis](#)
- ▶ [Dendritic Cells](#)
- ▶ [Mast Cells](#)
- ▶ [Neutrophil Oxidative Burst](#)
- ▶ [Regulatory T Cells](#)

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