

From innate to adaptive immune responses in contact hypersensitivity

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Purpose of review

To summarize recent findings that highlight the importance of the innate inflammatory immune responses in contact dermatitis and their role for the adaptive T-cell response to contact allergens. Implications for anti-inflammatory therapy based on recent reports are discussed.

Recent findings

Allergic contact dermatitis is studied widely in the mouse model. Recent work has identified an important role of innate pattern recognition receptors and innate immune cells in contact hypersensitivity. The role of skin dendritic cells has been studied with novel approaches for in-vivo depletion. New findings were made in the field of anti-inflammatory therapy either by uncovering new aspects of pathomechanisms or by the use of drugs that target different elements of the inflammatory cascade.

Summary

Inflammation is a pivotal element of allergic contact dermatitis. Studies in the mouse contact hypersensitivity model are beginning to shed light on the still largely unknown molecular mechanisms that enable contact allergens such as chemicals, metal ions and plant compounds to initiate the inflammatory innate immune response. This is a prerequisite for the adaptive immune response to occur. The recent progress in research points out the great potential of anti-inflammatory therapy covering a wide range of molecular targets.

Keywords

anti-inflammatory therapy, contact allergen, inflammasome, inflammation, Toll-like receptor

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Introduction

Allergic contact dermatitis (ACD) is well studied in the mouse contact hypersensitivity (CHS) model [1•]. In this disease, the activation of the innate immune system is triggered by contact allergens and generates an early inflammatory response in the skin [2•]. This is required to set off the adaptive immune response. T cells, predominantly of the Tc1, Th1 or Th17 subtype [2•,3•], then mediate the adaptive inflammatory response in the skin resulting in the characteristic clinical symptoms and signs. A great challenge in current research is to identify the mechanisms underlying the efficient triggering of the innate immune response by contact allergens.

Inflammation and irritant effect of contact allergens

The so-called irritant effect of contact allergens is the basis for the induction of an essential inflammatory response. Classical work by Grabbe *et al.* [4] demonstrated that

co-application of an irrelevant contact allergen, that is oxazolone, together with a suboptimal dose of the specific hapten 2,4,6-trinitrochlorobenzene (TNCB), was sufficient to trigger elicitation in TNCB-sensitized mice and *vice versa*. A recent study confirmed the importance of the strength of the irritant effect for the development and severity of CHS [5•]. Thus, a single low dose of 2,4-dinitrofluorobenzene (DNFB) resulted in irritant contact dermatitis (ICD) in C57BL/6 (B6) but not in Balb/c mice. This correlated with higher levels of the proinflammatory cytokines IL-1 β and IL-6 and lower levels of the immunosuppressive cytokine IL-10 in B6 mice compared with that in Balb/c mice. The primary CHS response that developed during the following days after a single hapten application and peaked on day 6–8 was stronger when higher doses of DNFB had been applied initially resulting in higher ICD. Using suboptimal concentrations of contact allergens dilutes their irritant effect below a critical threshold and eventually impacts on the T-cell response by inducing low zone tolerance (LZT). This tolerance is hapten specific and requires IL-10 producing regulatory

T cells for induction of immunosuppressive CD8+ Tc2 cells as effectors of LZT [6].

Pattern recognition receptors in innate immunity to contact allergens

The innate immune system uses different families of pattern recognition receptors (PRRs) to detect not only microbial but also endogenous danger signals [7]. The evidence that such receptors play a role in CHS is still scarce, but recent findings have demonstrated a role for members of the Toll-like receptor (TLR) and the Nod-like receptor (NLR) families of PRRs.

IL-1 β and IL-18 are two important proinflammatory cytokines in CHS. IL-18 acts upstream of IL-1 β and TNF- α in the induction of Langerhans cell migration [8 $\bullet$]. It has now been shown that the processing of the inactive pro-form of IL-1 β and IL-18 is mediated by the inflammasome, a cytosolic protein complex containing the NACHT, LRR and pyrin-family member (NALP)3, the adaptor protein apoptosis-associated speck-like protein (ASC) and procaspase-1 [9 $\bullet$]. The inflammasome was detected in human keratinocytes and dendritic cells [10 $\bullet\bullet$]. The active cytokines are generated via ASC-dependent caspase-1 activation in response to contact allergens such as TNCB. Thereafter, the cytokines are released by, for example, keratinocytes or dendritic cells in the skin. Whether contact allergens can directly activate NLRs like uric acid crystals [11], ATP or toxins [12], or whether they induce endogenous NLR ligands is unclear. Although one report demonstrated a significant decrease in the elicitation of TNCB-induced CHS in mice lacking ASC or NALP3 [13], another study found a reduction only in the early effector but not in the late effector phase following the challenge [10 $\bullet\bullet$]. Differences in the experimental protocols may account for the different findings.

A role for the lipopolysaccharide (LPS) receptor TLR4 in CHS has been suggested in a study using mice deficient in the mouse antimicrobial peptide cathelicidin Cnlp [14 $\bullet\bullet$]. These mice mounted an increased CHS response. Moreover, local administration of cathelicidin to the skin before contact allergen sensitization of wild-type mice prevented CHS suggesting an anti-inflammatory role of Cnlp. This inhibition was not observed in TLR4-deficient mice suggesting that Cnlp acts via TLR4.

Our recent work has identified a role for TLR2 and TLR4 in the induction phase of CHS (S.F. Martin *et al.*, unpublished observation). Mice with defects in IL-12R β 2 are resistant to CHS in response to TNCB, fluorescein isothiocyanate (FITC) and oxazolone upon concomitant deletion of TLR4. Similar results are obtained in mice lacking both TLR2 and TLR4. The defective CHS response was due to a failure of dendritic cells to sensitize for CHS.

It remains to be clarified how contact allergens are sensed by TLRs and NLRs. Our preliminary data show normal CHS in germ-free wild-type and IL-12R β 2-deficient mice. This indicates that contact allergens may induce the generation of endogenous ligands for TLRs in the tissue microenvironment of the skin.

Innate immune cells as effectors and regulators of contact hypersensitivity

A surprising result was reported when CHS was induced in T-cell-deficient and B-cell-deficient RAG2-/- mice. In this study, hapten-specific CHS to DNFB, oxazolone and TNCB was readily induced and the strength of the response was comparable to wild-type mice. The effector cells were identified as Thy1+ natural killer (NK) cells expressing Ly49C or Ly49I which are mostly found in the liver [15]. A role for the activating NK receptor NKG2D in CHS was demonstrated using anti-NKG2D antibodies before the challenge of sensitized mice. Whether the hapten specificity is due to conformational changes induced by hapten binding to major histocompatibility complex (MHC) class I molecules or bound peptides or by differential induction of stress-related NK receptor ligands following tissue damage by contact allergens recognized by activating or inhibitory NK receptors remains to be clarified.

Other innate immune cells also contribute to CHS. Thus, a recent study showed that mast cells are important suppressors of pathology associated with CHS to DNFB or urushiol from poison ivy by producing the immunosuppressive cytokine IL-10 [16 $\bullet\bullet$]. Mast cell deficient mice developed more intense and prolonged CHS responses. Engraftment of these mice with bone marrow derived wild-type but not IL-10 deficient mast cells resulted in normal CHS responses.

Dendritic cells are crucial in contact hypersensitivity: but which dendritic cell subset?

The first line of dendritic cells that interact with contact allergens in the skin are the Langerhans cells in the epidermis. They have been implicated together with the dermal dendritic cells to be the important carriers of allergen and topographical information as they migrate to the skin-draining lymph nodes. There, they activate naive allergen-specific T cells and imprint skin-specific homing receptors that enable the effector and memory T cells to find their way into the inflamed skin upon allergen challenge [1 $\bullet$,3 $\bullet$]. Recent studies using genetically engineered mice that allow depletion of Langerhans cells *in vivo* have questioned their importance for CHS. Depending on the depletion system, the haptens and the mouse strains that have been used Langerhans cells were found as being

required, dispensable or even immunoregulatory. The ongoing debate about their importance has recently been summarized [17[•]]. Using mice deficient in platelet-activating factor (PAF) receptor, a new study again claimed a minor role for Langerhans cells in CHS to DNFB [18[•]]. PAF is involved in the recruitment of leukocytes during inflammation. The authors found that in the PAF receptor deficient mice, CHS to DNFB was normal. Although migration of Langerhans cells to the skin-draining lymph nodes was compromised, dermal dendritic cell migration was unaffected. One of the drawbacks of some of these studies may be the use of high concentrations of contact allergens which are far from being physiological. Two elegant studies may help to resolve the controversies raised here. Bennett *et al.* [19[•]] addressed the issue of contact allergen concentration and hapten dependence. They confirmed their previous studies showing a requirement for Langerhans cells to generate an optimal CHS response to TNCB [20] by using oxazolone as a second hapten. It was shown that in the absence of Langerhans cells, haptens are inefficiently transported to the skin-draining lymph nodes. This resulted in inefficient priming of CHS effector T cells. Another study demonstrated the existence of Langerin+CD103+CD11b^{lo} dendritic cells, a new dendritic cell population in the dermis of mice, by comparing the two models used for in-vivo depletion of Langerhans cells [21^{••}]. Transgenic mice expressing the diphtheria toxin A subunit in Langerhans cells (HLang-DTA mice) lack epidermal Langerhans cells but still have dermal Langerin+ dendritic cells. In contrast, mice expressing the human diphtheria toxin receptor in Langerhans cells (Lang-DTREGFP knock-in mice) lose epidermal and dermal Langerin+ dendritic cells upon treatment with diphtheria toxin. The CHS response to DNFB was abrogated in mice lacking both Langerhans cells populations but was unaffected in mice lacking only epidermal Langerhans cells. In summary, epidermal Langerhans cells may be important for CHS responses when physiological allergen concentrations contact the skin. They may act in concert with the newly discovered dermal Langerhans cells, the origin of which remains to be elucidated. In the future, systems will likely be developed to deplete dermal dendritic cells once specific markers for this subset are identified.

It remains to be seen whether the different dendritic cell subsets in the skin have highly specialized tasks, which is not unlikely, and whether they can also fulfil similar functions in different tissue microenvironments such as the epidermis and the dermis.

Regulation of skin inflammation by the endocannabinoid system

Two recent reports have elucidated a role for the endocannabinoid system in inflammatory responses in CHS.

Cannabinoids act via the G protein-coupled cannabinoid receptors CB1 and CB2. These receptors are expressed on Langerhans cells and keratinocytes in the epidermis [22,23^{••}] and keratinocytes can produce and degrade endocannabinoids [23^{••}]. Endocannabinoids are elevated in skin following contact allergen treatment. Application of a CB2 receptor antagonist immediately after sensitization or upon challenge resulted in the marked suppression of oxazolone-mediated CHS and a reduced skin infiltration of eosinophils in chronic CHS [22]. In contrast, studies in mice deficient in both CB1 and CB2 revealed an increased CHS response following a single or repeated challenges with DNFB. Both receptors were involved as demonstrated by an increased ear swelling using CB1 or CB2 selective receptor antagonists [23^{••}]. Microarray-based profiling studies identified large numbers of chemokines and their receptors as being regulated differentially in wild-type or endocannabinoid receptor knockout mice treated with DNFB. Thus, the endocannabinoid system may contain skin inflammation by acting on the recruitment of inflammatory effector cells via the chemokine system. A highly interesting finding was the reduction of CHS upon topical application of the cannabinoid Δ^9 -tetrahydrocannabinol. These results encourage the use of cannabinoid receptor antagonists or inhibitors of endocannabinoid synthesis as new drugs for the treatment of contact dermatitis and possibly other cutaneous inflammatory diseases.

Anti-inflammatory therapy

Given the pivotal role of inflammation in CHS, strategies for anti-inflammatory therapy are being developed. Several drugs show impressive effects and target different elements of the innate and adaptive inflammatory cascade.

Recent studies have confirmed the therapeutic potential of immunosuppressive drugs like glucocorticoids or drugs that interfere directly or indirectly with the recruitment of effector cells by targeting the chemokine system or the adhesion molecules required for homing to the skin. In an elegant study, Cre/loxP-mediated selective ablation of the expression of glucocorticoid receptor in macrophages and neutrophils but not in T cells or keratinocytes prevented the downregulation of DNFB-induced CHS by the corticosteroid dexamethasone [24^{••}]. The effects were only detectable in the challenge but not in the sensitization phase. The dexamethasone-mediated reduction of the infiltration of oxazolone-treated skin by neutrophils and granulocytes was significantly impaired in mice expressing a DNA-binding mutant glucocorticoid receptor. This was most likely due to the lack of repression of inflammatory cytokine and chemokine expression upon glucocorticoid treatment. Other drugs that inhibit these pathways include nonsteroidal anti-inflammatory drugs

(NSAIDs) that target, for example, the NF- κ B pathway or COX-1 and COX-2. Furthermore, α -melanocyte-stimulating hormone (α -MSH) related peptides that act via G protein-coupled melanocortin receptors have been shown to target several inflammatory pathways [25[•]]. *N*-Acetyl-farnesyl-L-cysteine (AFC) inhibits G protein and G protein-coupled receptor signalling, thereby interfering with chemotaxis of neutrophils and other cells involved in inflammation. Topical application of AFC immediately after ear challenge inhibited DNFB-induced CHS, and the effect was restricted to the application site [26[•]].

Other drugs target the migration of dendritic cells from the skin or the homing of the CHS effector cells to the skin. As an example, the anti-inflammatory drug quina-crine was shown to inhibit the NF- κ B pathway and prevent the migration of epidermal dendritic cells [27[•]]. This correlated with the decrease in the NF- κ B-regulated cytokines TNF- α and IL-1 β and the chemokine CCL21 in skin and resulted in a marked reduction of CHS to DNFB.

In an interesting study, the fluorosugar 4-fluorinated *N*-acetylglucosamine (4-F-GlcNAc), a metabolic inhibitor of selectin ligand biosynthesis, was used to down-regulate expression of the skin-homing receptors E-selectin and P-selectin ligand on T cells and NK cells. The latter have been shown to participate in hapten-specific CHS responses [15]. Oral or intraperitoneal administration of 4-F-GlcNAc suppressed E-selectin ligand expression on T cells but not on NK cells [28^{••}]. The CHS response to DNFB was significantly reduced in wild-type but not in Rag1-/- mice. These data show a dominant role of skin-homing T cells in CHS in normal mice, whereas skin-homing NK cells mediate CHS in Rag1-/- mice that are unable to mount hapten-specific T-cell responses. Other approaches to interfere with effector cell homing include the use of monoclonal antibodies or small molecule inhibitors for adhesion molecules required for skin homing. The efficacy of these agents was demonstrated in DNFB-mediated CHS with antibodies blocking L-selectin or with efomycine M, a known inhibitor of E-selectin-mediated and P-selectin-mediated leukocyte rolling in blood vessels of inflamed tissues [29[•]]. L-Selectin mediates leukocyte homing to lymph nodes. In this study, it was demonstrated that efomycine M also interferes with L-selectin-mediated cell adhesion. Mice injected intravenously with the blocking antibody or efomycine M were sensitized with DNFB 1 h later and skin-draining lymph node cells of the sensitized mice were adoptively transferred to naive recipients on day 5 after sensitization. Ear challenge of the recipients showed a significant reduction when the lymph node cells were from pre-treated donors.

Pathogenic correlations with cutaneous drug hypersensitivity

Due to the similarities between cutaneous hypersensitivities to contact sensitizers and T-cell-mediated adverse drug reactions, similar mechanisms of innate immune activation may also underlie cutaneous drug hypersensitivity. Formal proof is still scarce, but an interesting pathway that may be employed by both types of agents is the phase II response, a cellular detoxification pathway in response to oxidative stress and electrophiles [30,31]. This pathway can be triggered by covalent binding of electrophiles such as contact sensitizers or drugs or their reactive metabolites to cysteine residues in the cytosolic protein Kelch-like *Escherichia coli* hemolysin (ECH) associated protein 1 (Keap-1). This protein binds to the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2). Upon modification of Keap-1, Nrf2 is released, translocates to the cytoplasm and activates genes containing antioxidant responsive elements (AREs). Interestingly, this pathway influences inflammation, the function of dendritic cells, production of IL-8 and expression of the chemokine receptor CCR7 as well as contact hypersensitivity and may also be important in the regulation of cutaneous drug reactions [32^{••},33^{••}].

Conclusion

Recent work mostly done in the mouse CHS model has revealed novel aspects of innate and adaptive immune responses. The exciting finding that PRRs are involved in contact dermatitis awaits the identification of ligands for these receptors. Contact allergens may be PRR ligands or may induce the production of such ligands in the skin microenvironment. Interestingly, mutations in innate immune receptors interfere with CHS. This suggests that genetic polymorphisms of these receptors may determine the susceptibility to ACD.

The increasing knowledge of the innate and adaptive pathomechanisms of CHS allows the identification of new targets for anti-inflammatory therapy.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 361–362).

- 1 Martin SF. In: Pichler WJ, editor. Drug hypersensitivity. Basel: Karger; 2007. pp. 34–46.
An update on studies in the mouse model covering different aspects of CHS.
- 2 Edele F, Esser PN, Lass C, et al. Innate and adaptive immune responses in allergic contact dermatitis and autoimmune skin diseases. *Inflamm Allergy Drug Targets* 2007; 6:236–244.

A timely overview of pathomechanisms, immune regulation and risk assessment strategies.

- 3 van Beelen AJ, Teunissen MB, Kapsenberg ML, de Jong EC. Interleukin-17 in inflammatory skin disorders. *Curr Opin Allergy Clin Immunol* 2007; 7:374–381.

A timely review of the important role of the IL-17 producing T cell subset in skin diseases.

- 4 Grabbe S, Steinert M, Mahnke K, *et al.* Dissection of antigenic and irritative effects of epicutaneously applied haptens in mice. Evidence that not the antigenic component but nonspecific proinflammatory effects of haptens determine the concentration-dependent elicitation of allergic contact dermatitis. *J Clin Invest* 1996; 98:1158–1164.

- 5 Bonneville M, Chavagnac C, Vocanson M, *et al.* Skin contact irritation conditions • the development and severity of allergic contact dermatitis. *J Invest Dermatol* 2007; 127:1430–1435.

This paper demonstrates the crucial role of the irritant effect of contact allergens with the extent of inflammation and its correlation with the severity of the ACD.

- 6 Seidel-Guyenot W, Perschon S, Dechant N, *et al.* Low zone tolerance induced by systemic application of allergens inhibits Tc1-mediated skin inflammation. *J Allergy Clin Immunol* 2006; 117:1170–1177.

- 7 Creagh EM, O'Neill LA. TLRs, NLRs and RLRs: a trinity of pathogen sensors that co-operate in innate immunity. *Trends Immunol* 2006; 27:352–357.

- 8 Antonopoulos C, Cumberbatch M, Mee JB, *et al.* IL-18 is a key proximal mediator of contact hypersensitivity and allergen-induced Langerhans cell migration in murine epidermis. *J Leukoc Biol* 2008; 83:361–367.

This paper expands the knowledge on IL-18 in CHS by demonstrating the hierarchy of IL-18, IL-1 β and TNF- α using knockout mice.

- 9 Petrilli V, Dostert C, Muruve DA, Tschopp J. The inflammasome: a danger • sensing complex triggering innate immunity. *Curr Opin Immunol* 2007; 19: 615–622.

This review summarizes the current knowledge on the structure and function of the inflammasome.

- 10 Watanabe H, Gaide O, Petrilli V, *et al.* Activation of the IL-1 β -processing • inflammasome is involved in contact hypersensitivity. *J Invest Dermatol* 2007; 127:1956–1963.

This study demonstrates the presence of inflammasomes in human keratinocytes and together with [13] shows their important role in CHS. Knockout mice for components of the inflammasome are used here.

- 11 Martinon F, Petrilli V, Mayor A, *et al.* Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature* 2006; 440:237–241.

- 12 Mariathasan S, Weiss DS, Newton K, McBride J, *et al.* Cryopyrin activates the inflammasome in response to toxins and ATP. *Nature* 2006; 440:228–232.

- 13 Sutterwala FS, Ogura Y, Szczepanik M, *et al.* Critical role for NALP3/CIAS1/ Cryopyrin in innate and adaptive immunity through its regulation of caspase-1. *Immunity* 2006; 24:317–327.

- 14 Di Nardo A, Braff MH, Taylor KR, *et al.* Cathelicidin antimicrobial peptides block • dendritic cell TLR4 activation and allergic contact sensitization. *J Immunol* 2007; 178:1829–1834.

This study shows that cathelicidin Cnlp has an anti-inflammatory role in CHS using Cnlp knockout mice and cathelicidin application to skin. Moreover, the effect of Cnlp is shown to be mediated by TLR4.

- 15 O'Leary JG, Goodarzi M, Drayton DL, von Andrian UH. T cell- and B cell- independent adaptive immunity mediated by natural killer cells. *Nat Immunol* 2006; 7:507–516.

- 16 Grimbaldston MA, Nakae S, Kalesnikoff J, *et al.* Mast cell-derived interleukin • 10 limits skin pathology in contact dermatitis and chronic irradiation with ultraviolet B. *Nat Immunol* 2007; 8:1095–1104.

An important study that demonstrates an immune regulatory role of IL-10 producing mast cells in the skin in CHS using mast cell deficient mice and reconstitution experiments with IL-10 deficient mast cells.

- 17 Bennett CL, Clausen BE. DC ablation in mice: promises, pitfalls, and chal- • lenges. *Trends Immunol* 2007; 28:525–531.

A timely summary of the controversial findings on the role of Langerhans cells from mouse studies using different systems to deplete epidermal Langerhans cells *in vivo*.

- 18 Fukunaga A, Khakhely NM, Sreevidya CS, *et al.* Dermal dendritic cells, and • not langerhans cells, play an essential role in inducing an immune response. *J Immunol* 2008; 180:3057–3064.

This study demonstrates that prevention of Langerhans cell migration does not impair CHS in PAF receptor deficient mice and supports a role for dermal dendritic cells in CHS.

- 19 Bennett CL, Noordegraaf M, Martina CA, Clausen BE. Langerhans cells are • required for efficient presentation of topically applied hapten to T cells. *J Immunol* 2007; 179:6830–6835.

This study expands on the role of Langerhans cells and shows their requirement for optimal effector T cell priming in CHS.

- 20 Bennett CL, van Rijn E, Jung S, *et al.* Inducible ablation of mouse Langerhans cells diminishes but fails to abrogate contact hypersensitivity. *J Cell Biol* 2005; 169:569–576.

- 21 Bursch LS, Wang L, Igyarto B, *et al.* Identification of a novel population of • Langerin+ dendritic cells. *J Exp Med* 2007; 204:3147–3156.

The study identifies a novel population of Langerin+ dendritic cells in the dermis of mice and demonstrates their important role in CHS.

- 22 Oka S, Wakui J, Ikeda S, *et al.* Involvement of the cannabinoid CB2 receptor and its endogenous ligand 2-arachidonoylglycerol in oxazolone-induced contact dermatitis in mice. *J Immunol* 2006; 177:8796–8805.

- 23 Karsak M, Gaffal E, Date R, *et al.* Attenuation of allergic contact dermatitis • through the endocannabinoid system. *Science* 2007; 316:1494–1497.

This study clearly shows a role for the endocannabinoid system in the regulation of CHS and encourages the development of receptor antagonists in therapy.

- 24 Tuckermann JP, Kleiman A, Moriggl R, *et al.* Macrophages and neutrophils are • the targets for immune suppression by glucocorticoids in contact allergy. *J Clin Invest* 2007; 117:1381–1390.

Using cell type-specific ablation of glucocorticoid receptors, this study elegantly identifies macrophages and neutrophils as the targets of glucocorticoid treatment in CHS.

- 25 Luger TA, Brzoska T. alpha-MSH related peptides: a new class of anti-inflam- • matory and immunomodulating drugs. *Ann Rheum Dis* 2007; 66 (Suppl 3): iii52–iii55.

This report demonstrates the great potential of a new class of anti-inflammatory peptides.

- 26 Gordon JS, Wolanin PM, Gonzalez AV, *et al.* Topical N-acetyl-S-farnesyl-L- • cysteine inhibits mouse skin inflammation, and unlike dexamethasone, its effects are restricted to the application site. *J Invest Dermatol* 2007; 128:643–654.

New finding showing that drugs interfering with G protein receptor signalling have potent anti-inflammatory properties.

- 27 Gorbachev AV, Gasparian AV, Gurova KV, *et al.* Quinacrine inhibits the • epidermal dendritic cell migration initiating T cell-mediated skin inflammation. *Eur J Immunol* 2007; 37:2257–2267.

The study identifies the anti-inflammatory effect of quinacrine in CHS based on its ability to block the NF- κ B pathway.

- 28 Gainers ME, Descheny L, Barthel SR, *et al.* Skin-homing receptors on effector • leukocytes are differentially sensitive to glyco-metabolic antagonism in allergic contact dermatitis. *J Immunol* 2007; 179:8509–8518.

An elegant study that expands the knowledge of the role of NK cells in CHS and demonstrates the different effects of therapies targeting T cell and NK cell-homing in CHS. Different susceptibility of T and NK cells to an inhibitor of selectin ligand synthesis is demonstrated.

- 29 Oostingh GJ, Ludwig RJ, Enders S, *et al.* Diminished lymphocyte adhesion • and alleviation of allergic responses by small-molecule- or antibody-mediated inhibition of L-selectin functions. *J Invest Dermatol* 2007; 127:90–97.

A study demonstrating that biologics and small molecule inhibitors can prevent CHS by inhibiting T cell homing to lymph nodes.

- 30 Park KB, Dalton-Brown E, Hirst C, Williams DP. Selection of new chemical entities with decreased potential for adverse drug reactions. *Eur J Pharmacol* 2006; 549:1–8.

- 31 Dinkova-Kostova AT, Holtzclaw WD, Kensler TW. The role of Keap1 in cellular protective responses. *Chem Res Toxicol* 2005; 18:1779–1791.

- 32 Natsch A, Emter R. Skin sensitizers induce antioxidant response element • dependent genes: application to the *in vitro* testing of the sensitization potential of chemicals. *Toxicol Sci* 2008; 102:110–119.

An innovative study that demonstrates the activation of the Keap-1/Nrf2 response by contact sensitizers but not irritants using a large number of chemicals and a luciferase reporter system.

- 33 Kim HJ, Barajas B, Wang M, Nel AE. Nrf2 activation by sulforaphane restores • the age-related decrease of T(H)1 immunity: role of dendritic cells. *J Allergy Clin Immunol* 2008; 121:1255–1261.

This study elegantly shows the role of antioxidant responses in contact hypersensitivity using Nrf2 knockout mice and the role of oxidative stress for the function of dendritic cells and Th1 immunity.