

Chapter 4

T Cell Responses to Contact Allergens

Hans Ulrich Weltzien, Stefan F. Martin, and Jean-François Nicolas

Abstract T lymphocytes are instrumental in the prevention of infections. With their antigen-specific T cell receptor (TCR), these cells recognize short peptides in the peptide-binding groove on MHC molecules of antigen-presenting cells. However, conventional T cells can also recognize non-peptide antigens including carbohydrates, phosphate groups, organic chemicals, and metal ions. The molecular basis of the interaction of TCR with these structures in the context of MHC has been partly solved. Organic chemicals and carbohydrates are recognized when bound to MHC-associated peptides, whereas metal ions are recognized due to their ability to form non-covalent coordination bonds with MHC molecules, bound peptides, and TCR. Peptide-independent metal ion recognition has also been described.

Abbreviations

ACD	Allergic contact dermatitis
APC	Antigen-presenting cell
CHS	Contact hypersensitivity
CMV	Cytomegalovirus
CSA	Cytokine secretion assay

H.U. Weltzien (✉)

Max-Planck-Institute for Immunobiology and Epigenetics, Freiburg, Germany

e-mail: huweltzien@yahoo.de

S.F. Martin

Allergy Research Group, Department of Dermatology and Venereology, University Medical Center Freiburg, Freiburg, Germany

e-mail: stefan.martin@uniklinik-freiburg.de

J.-F. Nicolas

Université Lyon1, UFR Lyon-Sud, INSERM U 1111—CIRI, IFR 128, Unité Allergologie et Immunologie Clinique, HCL, CH Lyon-Sud, Oullins 69921, France

e-mail: jean-francois.nicolas@chu-lyon.fr

DNBS	2,4-Dinitrobenzene sulfonic acid
hTCPA	Human T cell priming assay
LLNA	Local lymph node assay
MHC	Major histocompatibility complex
PBMC	Peripheral blood mononuclear cell
TCR	T cell receptor
TNBS	2,4,6-Trinitrobenzene sulfonic acid

Allergic contact dermatitis (ACD) is a delayed-type hypersensitivity response of the immune system to small, xenobiotic chemicals. These contact sensitizers or contact allergens activate initially the innate immune system to cause xenoinflammation (Martin 2012a, b). This essential inflammatory response in the skin eventually leads to the activation and migration of dendritic cells (DCs) from the skin to the draining lymph nodes. In the lymph nodes DCs that present the contact allergen in the context of MHC molecules activate naïve T cells expressing a contact allergen-specific T cell receptor (TCR) and drive their differentiation towards an effector T cell subset. The activated effector T cells can then enter the blood circulation. These events represent the sensitization phase of ACD. Encounter of the same contact allergen again induces skin inflammation which is required for the recruitment of the contact allergen-specific effector and memory T cells to the site of contact allergen exposure. The T cells then recognize their antigen on skin cells and exert cytotoxic effector functions and produce inflammatory mediators such as the cytokines IFN- γ , TNF- α , and IL-17. The result is the clinically evident eczematous skin reaction. This phase is called the elicitation phase of ACD.

Many studies have been performed in the mouse model of ACD, the contact hypersensitivity (CHS) model, in order to elucidate the immunological mechanisms underlying the activation of the innate and adaptive immune system by contact allergens (Martin 2013). Human *in vitro* studies have been conducted in parallel. The recent years have seen significant progress in our understanding of the molecular pathomechanisms that lead to xenoinflammation of the skin and activation of contact allergen-specific T cells (Martin 2012a, b; Martin et al. 2011).

4.1 T Cell Recognition of Organic Chemical Contact Allergens

The majority of contact allergens is represented by low molecular, protein-reactive chemicals. These may be of natural origin like urushiol from poison ivy or man-made synthetic compounds such as azo dyes, di- and trinitrochlorobenzene (DNCB, TNCB), or countless others. Contact sensitizers trigger a rather unspecific innate immune response via the generation of danger signals perceived, for example, by innate immune receptors and via effects mediated by induction of ROS

(Kaplan et al. 2012; Martin 2012a, b; Martin et al. 2011). The most specific response of the immune system to contact sensitizers is the T cell response. Antigen-presenting cells (APCs) can produce contact sensitizer-modified (haptenated) peptides from haptenated proteins and present these on MHC molecules. Alternatively direct modification of MHC-bound self-peptides on APCs can occur. The modified APCs then activate contact allergen-specific naïve T cells which then proliferate and differentiate to Tc1/Tc17 or Th1/Th17 effector cells of ACD.

The puzzling observation that the mammalian immune system is capable of specifically responding to such “unnatural” structures dates back to the first attempts to understand the molecular basis of immunological defense mechanisms in the early twentieth century.

Karl Landsteiner demonstrated the astonishing structural specificity of antibodies for low molecular chemicals coupled to autologous proteins (Landsteiner 1933) and introduced the term hapten (half antigen) for such molecules. He also was first to demonstrate hapten-specific skin sensitization in guinea pigs (Landsteiner and Jacobs 1935), a method still included in the methodology for risk assessment of potentially allergenic chemicals. The role of T cells and thymus in the adaptive immune response has been identified only much later (Gowans and Knight 1964; Osoba and Miller 1964) and in the following decade revealed the secret of MHC-restricted immune responses (Zinkernagel 1974).

It was then that contact hypersensitivity (CHS), or allergic contact dermatitis (ACD) as it was named by clinicians, was identified as a T cell-mediated, delayed-type hypersensitivity (DTH) reaction (Kimber and Dearman 2002). First studies in the mouse revealed that primary CHS to TNCB and oxazolone occurred 7 days after a single application of contact allergen. This response was transient. More efficient and long-lasting ear-swelling responses were observed after initial sensitization followed by ear challenge 7 days later. Passive CHS was established by the transfer of peritoneal exudate cells or lymph node cells from sensitized mice into naïve recipients that then received an ear painting with the contact allergen (Asherson and Ptak 1968). Consequently, hapten-reactive T cells were identified and shown to be MHC-restricted just like protein-specific ones (Shearer 1974) and, thus, to define the specificity of CHS.

In the verge of the identification of the T cell antigen receptor (TCR) (Haskins et al. 1984) and of MHC-bound peptides in class II (Buus et al. 1987) or class I MHC molecules (Falk et al. 1991) as TCR ligands, Ortmann et al. convincingly demonstrated that T cells recognized haptens when bound to MHC-associated peptides (Ortmann et al. 1992). Follow-up studies (Martin and Weltzien 1994) revealed that hapten-carrier peptides with allele-specific “anchoring motifs” (Rammensee 1995) served as high affinity anchors for haptens to specific MHC class I and II alleles (Martin et al. 1992, 1993a, b; Kohler et al. 1995). It was shown that antigen-presenting cells produced MHC class I-presented haptenated peptides from haptenated proteins delivered to the cytosol (Martin et al. 1993a, b) and that hapten-peptides extracted from class I MHC molecules of hapten-modified cells could sensitize target cells for lysis by hapten-specific cytotoxic T cell clones

(von Bonin et al. 1992). Studies with purified MHC molecules or cells deficient in MHC peptide loading excluded covalently hapten-modified MHC proteins (“altered self”) as major TCR ligands (von Bonin et al. 1992, 1993). The *in vivo* relevance of these findings was shown by sensitization of mice with TNP-peptide-pulsed dendritic cells for allergic contact hyperreactivity to TNCB (Martin et al. 2000).

A contribution of the peptide carrier to antigenic specificity was negligible for haptens in central peptide positions, but was clearly demonstrated for haptens attached to peripheral amino acids. This was taken to indicate a possible role of haptens in the induction of autoimmunity (Martin et al. 1995).

The transferability of the hapten-peptide paradigm to human allergy has been evaluated in two systems, i.e., hyperreactivity to penicillins and allergic contact dermatitis to nickel (Ni). In perfect analogy to the mouse model, E. Padovan demonstrated that T cell clones from patients allergic to different penicillins reacted to penicilloyl peptides in an HLA-restricted, penicillin- and position-specific manner (Padovan et al. 1997).

4.2 T Cell Recognition of Metal Ions

The picture became more complex when T cell reactivities to metal ions such as nickel were investigated. Unlike chemically reactive haptens, Ni ions engage in non-covalent, i.e., reversible, coordination complexes predominantly with nitrogen residues in histidine or arginine. Thus, despite the existence of large collections of Ni-reactive T cell clones (Kapsenberg et al. 1987; Moulon et al. 1993; Sinigaglia et al. 1985), T cell antigenic nickel epitopes could only be identified upon the expression of nickel-specific human TCR in TCR-deficient mouse hybridoma cells (Vollmer et al. 1999). Besides resulting in long-lived, easy to culture cell lines, this system allowed the systematic mutation of the antigen-binding CDR3 regions in TCR α - and β -chains and, hence, the localization of contact sites for nickel in TCR and HLA protein.

These studies revealed two principally different ways of TCR interactions with Ni plus HLA: for one TCR, Lu et al, indeed, showed the combination of defined peptide and HLA haplotype to be essential for Ni recognition (Lu et al. 2003). However, a different TCR recognized nickel HLA haplotype specific but apparently independent of the nature of associated peptides (Gamerding et al. 2003). In this case histidine residues in defined positions of variable TCR and HLA regions were identified as coordination sites for a Ni-mediated, peptide-independent TCR-HLA complex, which effectively induced TCR signaling. Moreover, it was shown that Ni ions may be transferred from complexes with other proteins such as human serum albumin to coordination sites provided by TCR-HLA combinations (Thierse et al. 2004, 2005).

4.3 T Cell Receptor and Epitope Recognition

The exquisite antigen specificity of the T cell response to contact sensitizers has raised interest in the development of T cell-based assays for the *in vitro* identification of these chemicals (Martin et al. 2010). This specificity is illustrated by the ability of T cell clones to differentiate β -lactam antibiotics with different side chains and the ability to differentiate TNP- and DNP-modified peptides.

The antigen specificity of the T cell receptor is generated during T cell development in the thymus. In the developing T cells, somatic rearrangement of gene segments coding for variable (V) and joining (J) segments in the TCR α chain and additional D segments in the TCR β chain with constant (C) segments leads to VJC TCR α and VDJC TCR β chains that are clonally distributed after having undergone positive and negative selection. These processes generate a broad repertoire of clonally distributed TCR containing about 10^{14} different antigen specificities. Interestingly, clonally distributed antigen-specific receptors have been identified in lymphocyte lineages of lamprey where so-called variable lymphocyte receptors (VLR) determine antigen specificity. Based on very different diversification mechanisms 10^{14} – 10^{17} , different specificities may be generated which is similar to the diversity of TCR specificities (Boehm et al. 2012).

When foreign antigens are encountered, only T cell clones with specific receptors are selectively expanded from the highly diverse repertoire. The diversity of the antigen-selected repertoire is influenced by a variety of factors. These include the number of epitopes, the affinity of peptide binding to MHC and to the TCR.

Contact allergens turn self into foreign by the generation of chemically modified self-peptides. Moreover, it is also possible that altered processing of self-proteins occurs due to the modification of recognition sites for the proteasome and endolysosomal proteases that are involved in antigen processing for MHC class I and MHC class II presentation. Whether this may lead to the recognition of neoantigens, cryptic peptides that have not been presented to developing T cells in the thymus and thus have not contributed to thymic selection, is so far unknown. It is conceivable that most of the T cells involved in chemical-induced allergies recognize the chemical. However, it is possible that T cells primed by haptenated peptides may also react to the unmodified self-peptide. Such reactivities may underlie the vitiligo associated with melanoma therapy using the topical application of the contact sensitizers DNCB or DPCP. In that case the reactivity of cytotoxic T cells to unmodified self-peptides resulted in the killing of healthy melanoma cells resulting in depigmentations as a side effect observed in this therapy (Henderson and Ilchyshyn 1995). It remains to be determined whether the peptides recognized in these T cell responses are the non-haptenated carrier peptide sequences or peptide mimotopes of the haptenated peptides. A recent study has proven the existence of such peptide mimotopes (Yin et al. 2012). An HLA-DR52c-restricted nickel-reactive human T cell clone, ANi2.3, isolated from a Ni-allergic patient

(Lu et al. 2003), was used to screen engineered peptide libraries for peptides recognized in the presence of Ni. Surprisingly, only Ni-independent peptide mimotopes instead of a self-peptide complexed to nickel were recognized by the T cell clone. It was shown that the TCR V β CDR3 region interacted especially with a conserved lysine residue present in position 7 of the DR52c-binding nonameric peptides, and it was suggested that this lysine mimics Ni in the natural TCR ligand. The CDR3 loop extends into the region of the DR52c to interact with conserved residues in a panel of mimotope peptides and residues of the DR52c α 1 and β 1 helices. Interestingly, an aspartic acid residue was crucial for the peptide recognition and could not be replaced by a glutamic acid residue.

Biacore measurements and crystal structure analyses revealed that ANi2.3 TCR recognizes mimotope peptides with affinities in the range of normal peptide antigen recognition and that it was oriented in the typical diagonal orientation over the peptide-MHC complex. These data show that this Ni-specific TCR interacts with the positively charged Ni²⁺ complexed to a self-peptide and that Ni and maybe also other metals are most likely accommodated by an acidic pocket formed by the α 1 and β 1 chains of DR52c in the peripheral region of the peptide-binding groove where the conserved positively charged lysine residue in position 7 of the peptide mimotopes was located. Similarly, a recent study demonstrated the peptide-dependent recognition of beryllium by HLA-DP-restricted CD4+ T cells and identified peptide mimotopes with amino acid residues in defined positions that coordinate beryllium in cooperation with HLA-DP. HLA-DP tetramers loaded with such mimotopes plus beryllium as well as an endogenous peptide containing the core motif were used and revealed a high frequency of specific CD4+ T cells in patients with chronic beryllium disease (Falta et al. 2013).

The use of peptide libraries in combination with multimeric MHC molecules for the identification of unknown T cell epitopes is very attractive and may be done by the baculovirus/insect cell approach. A recent study reported the generation of plasmid-coded combinatorial peptide libraries co-transfected with MHC molecules into COS-7 cells for the identification of target antigens for CD8+ T cells (Siewert et al. 2012). The use of such approaches to also analyze the recognition of xenobiotic chemicals by T cells is of great interest and has a great potential as described for nickel and beryllium (Falta et al. 2013; Yin et al. 2012). It is likely that peptide mimotopes can be identified also for organic contact allergens and drugs mediating T cell-mediated adverse reactions. It may also be feasible to produce libraries of haptenated peptides that would provide a useful tool to dissect contact allergen-specific T cell responses. Such studies should help to understand the nature of the self-peptide-selected TCRs that react to such chemicals and to explain why they become chemical reactive.

4.4 Innate Immune Responses to Contact Allergens and Drugs

It is to be expected that T cell-mediated adverse drug reactions (ADR) follow similar basic mechanistic principles as T cell-mediated ACD. The culprit drugs must activate both the innate and the adaptive immune system. The nature of the danger signals generated remains to be determined, and tissue-specific effects have to be considered. Drugs are often given orally and end up in tissue microenvironments that are very different from the skin. Therefore, the innate immune responses in the gastrointestinal (GI) tract and the liver may be different than those triggered by contact sensitizers in the skin. However, in order to prime naïve drug-specific T cells, danger signals will also be needed to eventually activate DCs that present the drugs to T cells in the local lymph nodes. The drug acetaminophen (APAP) can induce drug-induced liver injury (DILI). The mechanisms by which the inflammatory response is triggered are strikingly similar to the mechanisms triggered by contact allergens but involving in part other cell types, innate immune receptors, and danger signals (Martin 2012a, b). APAP triggers damage of liver cells resulting in the release of self-DNA which then acts as an endogenous danger signal (DAMP). This DAMP triggers TLR9 on sinusoidal liver endothelial cells which release ATP as another endogenous danger signal perceived via the P2X7R. P2X7R triggering then results in the activation of the NLRP3 inflammasome and formation of mature IL-1 β and IL-18 (Hoque et al. 2012; Imaeda et al. 2009). Interestingly, up to now there is no evidence for the activation of conventional APAP specific T cells in this liver disease.

The fact that there are often skin manifestations after oral drug intake is very interesting and may indicate a transport of the drugs from the GI tract into the skin. Carrier molecules such as human serum albumin that is also found in the skin may play a role here. Whether the T cells responsible for the skin phenotype are primed in the skin-draining lymph node and thereby acquire a skin-homing receptor profile or whether they home to the skin due to the innate inflammatory response induced by the drugs is so far unknown.

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