Lymphocyte Activation in Cutaneous Drug Reactions

Michael Hertl and Hans F. Merk
Department of Dermatology, RWTH Aachen, Aachen, Germany

Peripheral blood lymphocytes from both drug-induced immediate and delayed cutaneous hypersensitivity reactions frequently can be stimulated *in vitro* with the particular culprit drug. Immunohistochemical analysis has identified CD8+ T cells as the predominant epidermal T-cell subset in drug-induced maculopapular and bullous eruptions and in patch-test reactions to β-lactam antibiotics. β-lactam–specific peripheral and epidermal T lymphocytes from bullous exanthems were predominantly T-cell receptor α/β+, CD8+, CD4−. Three CD8+ epidermal T-cell clones from penicillin-induced bullous exanthems displayed a TH1-like cytokine pattern and proliferated in an antigen- and major histocompatibility complex–specific manner. These epidermal T-cell clones were cytotoxic against autologous B cells upon stimulation through the T-cell receptor and against epidermal keratinocytes in lectin-induced cytotoxicity assays. In contrast, peripheral T-cell lines from patients with penicillin-induced urticarial exanthems were predominantly T-cell receptor α/β+, CD4+, CD8− and displayed a Th2-like cytokine pattern. CD8+ dermal T cells from a sulfamethoxazole-induced bullous exanthem proliferated *in vitro* in response to sulfamethoxazole. This T-cell proliferation was significantly increased in the presence of microsomes, which suggests that microsomal enzymes, such as cytochrome P450 enzymes, generate highly reactive metabolites which are the nominal antigens for T-cell activation. In summary, drugs may be processed and presented in different ways, which is reflected by the observation that Th1-like CD8+ T cells are primarily activated in delayed cutaneous hypersensitivity reactions, whereas Th2-like T-cell responses are present in patients with drug-induced urticarial exanthems. ***Key words: CD8+ T cells/drug hypersensitivity/lymphocyte transformation/major histocompatibility complex/cytochrome P450/haptens.***
J Invest Dermatol 105:95S–98S, 1995

Drug-induced cutaneous hypersensitivity reactions represent a variety of distinct clinical entities [1]. Although immediate-type hypersensitivity reactions, such as urticarial exanthems and anaphylaxis, are mediated by drug-specific IgE antibodies, the pathogenesis of delayed-type hypersensitivity reactions, such as morbilliform or bullous eruptions, has not been fully elucidated [2]. Sulfonamides, β-lactam antibiotics, anti-epileptic agents (particularly phenytoin), and nonsteroidal anti-inflammatory drugs are the major causes of drug-induced toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (reviewed in [3]). There is *in vivo* and *in vitro* evidence that T lymphocytes are involved in the pathogenesis of drug-induced cutaneous reactions, in that peripheral blood mononuclear cells (PBMC) from patients with drug-induced immediate-type reactions (urticaria) and delayed hypersensitivity reactions (morbilliform and bullous exanthems) frequently can be stimulated *in vitro* with the causative drug [4,5]. In addition, several histologic studies have demonstrated that the inflammatory infiltrate in drug-induced delayed cutaneous hypersensitivity reactions is primarily composed of lymphocytes. This brief review focuses on current studies on the pathogenesis of morbilliform and bullous exanthems, which include the most severe drug-induced cutaneous hypersensitivity reactions.

Reprint requests to: Dr. Michael Hertl, Department of Dermatology, Medical Faculty, RWTH Aachen, Pauwelsstrasse 30, D-52074 Aachen, Germany.

Abbreviations: LTT, lymphocyte transformation test; SMX, sulfamethoxazole; TEN, toxic epidermal necrolysis.

IN VIVO STUDIES

Immunohistochemical Findings Immunohistologic studies in drug-induced TEN, Stevens-Johnson syndrome, and erythema multiforme have shown that the dermal infiltrate is composed mainly of CD4+ T lymphocytes, whereas mononuclear cells disposed along the epidermal junction and migrating into the epidermis are CD8+ T lymphocytes [6–9]. Studies by Osawa *et al* [10] demonstrated a predominance of epidermal CD8+ T cells in drug-induced bullous exanthems, whereas lichen planus-like and morbilliform exanthems were characterized by both CD4+ and CD8+ epidermal and dermal T cells. No definitive data are available regarding the frequency of drug-specific T cells in the epidermal and dermal infiltrate. The clinical and histologic picture of TEN shows striking similarity to that of severe graft *versus* host reaction [9]. Cell-mediated cytotoxicity of lymphocytes against epidermal cells may explain the pathologic finding of "satellite cell necrosis" (necrotic keratinocytes adjacent to mononuclear cells) in the early phase of drug-induced TEN as in acute cutaneous graft *versus* host reaction [9]. Most immunohistochemical studies of TEN have also found variable degrees of up-regulation of intercellular adhesion molecule-1 (ICAM-1) and human leukocyte antigen (HLA)-DR on keratinocytes in involved skin, which is presumably due to cytokine secretion by infiltrating T cells [7,8,11]. Several

0022-202X/95/$09.50 • SSDI0022-202X(95)00186-O

studies have also characterized the inflammatory infiltrate of fixed drug eruptions [12]. As in the above-mentioned bullous exanthems, CD8+ T cells were the predominant epidermal subset and were still detectable at the epidermal junction 3 weeks after the resolution of fixed drug eruptions [13]. This persistence of potentially drug-specific T cells in the skin may explain why fixed drug eruption reappears at the same site upon rechallenge with the particular drug. A focal dysregulation of the interferon-γ (IFN-γ)–induced up-regulation of ICAM-1 on epidermal keratinocytes has also been implicated as a pathogenic factor in fixed drug eruptions [14].

IN VITRO STUDIES

Lymphocyte Transformation Test (LTT). The LTT has a long history as an *in vitro* assay for detection of drug-specific lymphocyte activation [4,5,15,16]. PBMC from patients with cutaneous hypersensitivity reactions are co-cultured with the causative agents, and lymphocyte activation is determined after 5–7 d by the incorporation of radioactive thymidine [5,15]. This test has been reported to give positive results with a variety of drugs, including β-lactam antibiotics, antiepileptic agents, sulfonamides, nonsteroidal anti-inflammatory drugs and others [4,5,15,16]. Performing phenotypic analysis, Koponen *et al* [17] found that CD4+ T cells were the major T-cell subset activated upon co-culture with penicillins *in vitro*. The LTT provided some evidence that penicilloyl, the major metabolite of benzylpenicillin, plays a role as a nominal antigen in that PMBC of some penicillin-allergic patients were activated *in vitro* by both benzylpenicillin and penicilloyl [15]. PBMC from penicillin-allergic individuals were occasionally activated by the first-generation cephalosporin cephalothin, which is presumably hydrolyzed to a cephaloyl derivative that is structurally related to penicilloyl [15]. A major problem associated with interpretation of LTT results is the lack of appropriate controls, i.e., PBMC from healthy controls treated with the investigated drug but without allergic reaction. Drug-induced lymphocyte proliferation is frequently low, which makes it hard to distinguish between positive and false-negative results. This is important because PBMC from healthy donors can occasionally be stimulated *in vitro* by the tested drug [5,15]. In our experience, the PBMC from six of 25 healthy volunteers were stimulated *in vitro* by benzylpenicillin; all of the responders had been treated with β-lactam antibiotics in the past [15]. Stejskal *et al* [18] also found benzylpenicillin-specific lymphocyte proliferation in the LTT and benzylpencillin-specific IgG antibodies in healthy individuals with occupational exposure to penicillins. Another disadvantage of the LTT is the limited knowledge of the frequency of drug-specific precursor T cells in the peripheral blood. The lack of reproducibility of T-cell stimulation by the causative drug in the LTT may result from low frequency of the drug-specific precursor cells. This is reflected by the observation of Roujeau *et al* [16] that the drug-induced proliferation of PBMC from TEN patients, seen *in vitro* at the onset of clinical symptoms, was virtually absent months later.

Generation of Drug-Specific Peripheral and Lesional T-Cell Clones From Patients With Morbilliform and Bullous Drug Eruptions In a recent study, exclusively CD8+ epidermal T-cell clones were isolated from β-lactam–induced bullous exanthems and patch-test reactions [11]. Three epidermal CD8+ T-cell clones proliferated to the particular β-lactam antibiotic in a major histocompatibility complex (MHC)-restricted fashion and produced TH1-pattern cytokines after activation [11]. Identical observations were made with peripheral β-lactam–specific T-cell clones from patients with morbilliform exanthems, which were exclusively CD8+ and proliferated in response to benzylpenicillin and to its major metabolite penicilloyl [19]. These clones also secreted Th1-like cytokines. The predominant generation of epidermal CD8+ T lymphocytes is unlikely to be a culture artifact in that CD4+ antigen-specific T-cell clones were predominantly generated from positive epicutaneous test reactions to fragrances* and CD4+ T-cell lines specific for tetanus toxoid from the peripheral blood of immunized donors [19]. In addition, more CD4+ than CD8+ peripheral T-cell lines were derived from patients (n = 3) with penicillin-induced urticarial exanthems (unpublished observation). The CD4+ T-cell lines displayed a TH2-like cytokine pattern in that they produced interleukin-4 (IL-4), no IFN-γ, and low amounts of IL-2. These CD4+ T cells may provide help for B cells to produce penicillin-specific IgE antibodies, which have a critical function in drug-induced immediate hypersensitivity reactions.

Current concepts attribute two different functions to CD8+ T cells; an IFN-γ–producing subset plays a role in cell-mediated cytotoxicity, and an IL-4–producing population provides help for IgE production by B cells and suppresses the activation of CD4+ helper Th1-like cells [20]. Because the epidermal-derived CD8+ T-cell clones were cytotoxic *in vitro* against epidermal keratinocytes and B cell lines [11], we speculate that they act as cytotoxic effector cells *in vivo*. Several studies have shown that CD8+ T-cell lines with cytotoxic activity can mediate delayed-type inflammatory reactions *in vivo* [21]. It is unclear why drug-specific CD8+ T lymphocytes preferentially localize in the epidermis. This phenomenon is not unique to drug reactions; epidermal CD8+ T cells were also expanded from lesional skin of patients with psoriasis vulgaris [22] or graft versus host disease [23]. CD8+ T lymphocytes have also been identified as effector cells in allergic contact dermatitis [24] and in humans allergic to the hapten poison ivy [25]. All β-lactam–specific epidermal CD8+ T-cell clones produced significant amounts of IFN-γ, which is known to induce up-regulation of ICAM-1 on endothelial cells and keratinocytes [26,27]. Up-regulation of ICAM-1 on keratinocytes in cutaneous drug reactions may be due to the release of IFN-γ by infiltrating T cells [27,28]. ICAM-1, the ligand for leukocyte function-associated antigen-1 on T cells, is a critical adhesion molecule for the homing of T lymphocytes into the skin [26]. Interaction of leukocyte function-associated antigen-1 and ICAM-1 also plays a critical role in T-cell–mediated cytotoxicity [29]. Epidermal T cells isolated from various drug-induced bullous exanthems (β-lactam antibiotics, n = 5; carbamazepine, n = 2; sulfamethoxazole, n = 2; acetylsalicylic acid, n = 1) were uniformly T-cell receptor α/β+, which is in keeping with the findings of Foster *et al* [30].

Role of Drug Metabolism in the Formation of the Nominal Antigens Most drugs are metabolized by cytochrome-P450–dependent enzymes to highly reactive derivatives, which may be detoxified or act as a toxic agent (or immunogenic hapten) [2,4]. The activities of these P450-dependent isoenzymes exhibit genetic polymorphism, and the genes of more than 300 isoenzymes have already been cloned; this may explain the heterogeneity of the individual response to the particular drug.

Phenytoin is metabolized by cytochrome-P450–dependent enzymes into a highly reactive arene-oxide metabolite, which is detoxified primarily by epoxide hydrolases [31,32]. This compound is highly toxic to cells but may also bind to proteins. The increased toxicity of phenytoin to lymphocytes of phenytoin-allergic patients indicates that a polymorphism in the activity of the epoxide hydrolase may be the cause for this syndrome [31]. Shear and Spielberg [31] proposed the use of the lymphocyte toxicity assay for *in vitro* diagnosis of the phenytoin hypersensitivity syndrome because PBMC from patients with this syndrome are highly susceptible to the toxic effects of cytochrome-P450–dependent metabolites of most (not chemically related) anti-epileptic drugs, including phenytoin, carbamazepine, and phenobarbital (though not valproinic acid).

Sulfamethoxazole (SMX) is metabolized by acetylation to N4-cetyl-SMX and by cytochrome P450 to 5-hydroxy-SMX or to a reactive hydroxylamine [33,34]. The hydoxylamine derivative may be detoxified by glutathione synthetase or may bind to macromol-

* Niederau D, Hertl M, Boecker C, Geisel J, Merk H: CD4+ antigen-specific cytotoxic T lymphocytes are present in contact hypersensitivity reactions to fragrances (abstr). *J Invest Dermatol* 102:480A, 1994.

ecules to form an immunogen [33]. Cytochrome-P450–dependent SMX metabolites may be important in the pathogenesis of SMX-induced hypersensitivity reactions because an SMX-specific CD8+ dermal T-cell clone from an SMX-induced bullous exanthem showed a significantly increased proliferation to SMX in the presence of microsomes rich in cytochrome P450 [34]. This observation suggests that cytochrome-P450–dependent SMX metabolites were relevant T-cell antigens. This finding is of particular interest because recent studies have indicated that some patients with sulfonamide-induced bullous cutaneous eruptions exhibit reduced N-acetylating capacity.‡ In addition, patients with increased cytochrome-P450–dependent metabolism of sulfonamides to hydroxylamine derivatives have an increased risk to develop drug-induced hypersensitivity reactions [35]. Analogous to the findings in the phenytoin hypersensitivity syndrome, the toxicity of the hydroxylamine metabolite of SMX was greatest for PBMC from SMX-allergic patients [2,34]. Kalish *et al* [36] have also demonstrated that T lymphocytes reactive to SMX are present at low frequencies in the peripheral blood of patients with drug eruptions secondary to treatment with sulfonamides. Mauri-Hellweg *et al* observed an increased expression of CD25 (IL-2R) and HLA-DR (MHC II) on peripheral CD4+ and CD8+ T cells from allergic donors stimulated *in vitro* with SMX.§ Supernatants from these cultures contained high amounts of IL-5, which was presumably produced by SMX-activated T cells. *In vitro* cultures with SMX induced the preferential expansion of CD25+ T-cell receptor Vβ17+ T cells, suggesting that drug-activated T cells displayed a limited T-cell receptor usage.

Niederau *et al* [37] have also provided evidence for the role of cytochrome-P450–dependent enzymes in the generation of the nominal antigens recognized by lymphocytes from pyrazolone-sensitized individuals. PBMC from eight patients with hypersensitivity reactions to the pyrazolone derivatives metamizole, propyphenazone, and phenazone were strongly stimulated by these drugs in the presence of cytochrome-P450–enriched microsomes, whereas co-culture with the parent drugs alone caused absent or significantly less lymphocyte proliferation.

Penicillins hydrolyze spontaneously to form a penicilloyl group (which can covalently bind to either amino or sulfhydryl groups of proteins) and to the so-called minor determinants [38–40]. The relevance of the binding of penicilloyl to albumin has been confirmed *in vivo* in that patients receiving benzylpenicillin showed a dose-dependent saturation of serum albumin with penicilloyl [40]. As mentioned earlier, penicilloyl can stimulate penicillin-specific T cells [15,34]. The penicillin-specific IgE antibody response is heterogeneous in that antibodies against the common β-lactam ring structure and various side-chain determinants are present in the sera of penicillin-allergic patients [39]. In many instances, only antibodies against the side-chain determinants of β-lactam antibiotics are found [9,18]. Side-chain–specific lymphocyte proliferation has been demonstrated in individuals with occupational exposure to the ampicillin derivative α-aminobenzylpenicillin ester (bacampicillin). In these patients, PBMC proliferated in response to the N-acylamido side chain and the ester group of the bacampicillin molecule, but not to benzylpenicillin, penicillin V, or 6-aminopenicillanic acid [18]. In addition, PBMC from ampicillin-allergic patients were activated *in vitro* by ampicillin but not by benzylpenicillin [41,42]. Penicilloyl-specific IgG antibodies can be found in the sera of healthy individuals treated with penicillins [40]. However, the presence of benzylpenicillin-specific IgE antibodies is generally linked to the occurrence of penicillin-induced allergic reactions [40].

‡ Dietrich A, Kawakubo Y, Rzany B, Schöpf E: Patients with severe cutaneous drug reactions (EM,SJS,TEN) have a reduced N-acetylating capacity (abstr). *J Invest Dermatol* 100:519A, 1993.

§ Mauri-Hellweg D, Bettens F, Mauri D, Brander C, Hunziker T, Pichler W: Activation of drug-specific CD4+ and CD8+ T cells in individuals allergic to sulfonamides, phenytoin and carbamazepine (submitted).

Molecular Mechanisms of Drug-Induced T-cell Activation

Haptens, such as drugs and small-molecular-weight contact sensitizers, interact with proteins by a variety of chemical reactions and have a broad range of physical properties [4,43]. This diversity in hapten chemistry is probably reflected in diversity of antigen processing and presentation. Functional data suggest that drugs preferentially activate CD8+ T cells but also activate CD4+ T cells [11,19,34]. The predominant activation of CD8+ T cells suggests that the processing of drug-conjugated proteins proceeds by the endogenous pathway. Because most drugs are exogenous substances, they may be internalized, conjugated to intracellular proteins, and presented by MHC I molecules to CD8+ T cells. The penicilloyl moiety, the major penicillin metabolite [38,39], seems to play a role in penicillin-specific T-cell activation, as benzylpenicillin-specific CD8+ T-cell clones were also significantly stimulated by penicilloyl [34]. Pichler [5] reported that PBMC from penicillin-allergic patients can be optimally stimulated *in vitro* with unmodified benzylpenicillin. In some instances, less vigorous *in vitro* lymphocyte stimulation could also be achieved with benzylpenicillin coupled to albumin [5]. Bell and Pichler [44] found that glutaraldehyde-fixed antigen-presenting cells acted as sufficient antigen-presenting cells for penicillin-induced T-cell proliferation, suggesting that penicillin can bind directly to MHC molecules or MHC-associated endogenous peptides. Direct interaction with MHC II molecules has been demonstrated for the hapten gold [45]. In our experience, paraformaldehyde fixation significantly diminished the ability of Epstein-Barr virus–transformed B-cell lines to present benzylpenicillin to benzylpenicillin-specific CD8+ T-cell clones, suggesting that processing was required [11]. Regarding the nature of the complete antigen, Claas *et al* [46] demonstrated that benzylpenicillin-treated lymphocytes are no longer susceptible to the cytotoxicity of HLA typing sera against certain MHC I haplotypes. This observation suggests that penicillins bind to MHC I antigens. Sparse evidence for the preferential association of drugs with certain MHC haplotypes is given from linkage studies based on the MHC haplotypes of patients with drug-induced cutaneous hypersensitivity reactions [47]: sulfonamide-induced TEN is associated with HLA-A29, HLA-B12, and HLA-DR7; and so is sulfonamide-induced Stevens-Johnson syndrome (HLA-A29, HLA-B44, HLA-DR7). Herpes simplex–associated erythema multiforme is linked to HLA-B12 and HLA-DQ3.

SUMMARY AND CONCLUSIONS

Drug-specific CD8+ T lymphocytes are present in the peripheral blood and involved skin of patients with drug-induced delayed cutaneous hypersensitivity reactions, such as morbilliform and bullous exanthems. The observed predominance of cytotoxic epidermal CD8+ T lymphocytes in drug-induced bullous exanthems suggests that this particular T-cell subset plays a role in the pathogenesis of drug-induced blister formation. In contrast, there is evidence that CD4+ T cells with a TH2-like cytokine pattern are preferentially activated in IgE-mediated cutaneous drug reactions. The metabolism of the many drugs, for example by cytochrome-P450–dependent enzymes, is critical in the formation of the nominal T-cell antigens, as demonstrated in the case of SMX-dependent T-cell activation. Because of the chemical properties of haptenic drugs, there seems to be a diversity of processing and presentation pathways of drugs, which is reflected in the activation of both CD8+ TH1-like cells in bullous exanthems and CD4+ TH2-like T lymphocytes in IgE-mediated immediate hypersensitivity reactions.

We thank Drs. Stephen I. Katz and Mark C. Udey for their critical review of the manuscript. This work was supported by grants He 1602/3-1 and He 1602/3-2 from the Deutsche Forschungsgemeinschaft, Bonn, Germany.

REFERENCES

1. Prussick R, Knowles S, Shear NH: Cutaneous drug reactions. *Curr Probl Dermatol* 3:81–124, 1994

2. Kalish RS: Drug eruptions: a review of clinical and immunological features. *Adv Dermatol* 6:221–237, 1991
3. Roujeau JC: The spectrum of Stevens-Johnson syndrome and toxic epidermal necrolysis: a clinical classification. *J Invest Dermatol* 102:28S–30S, 1994
4. Merk H, Schneider R, Scholl P: Lymphocyte stimulation with drug-modified microsomes. In: Eastbrook RW, Lindlaub E, Oesch F, de Weck AL (eds.). *Toxicological and Immunological Aspects of Drug Metabolism and Environmental Chemicals*. Schattauer, Stuttgart, Germany, 1987, pp 211–220
5. Pichler WJ: Der Lymphozytentransformationstest in der Diagnostik von unerwünschten Arzneimittelreaktionen. *Z Hautkr* 68:789–794, 1993
6. Tonnessen MG, Harrist TJ, Wintroub B: Erythema multiforme: microvascular damage and infiltrates of lymphocytes and basophils. *J Invest Dermatol* 10:282–287, 1983
7. Miyauchi H, Hosokawa H, Akaeda T, Iba H, Asada Y: T cell subsets in toxic epidermal necrolysis. *Arch Dermatol* 127:851–855, 1991
8. Heng MCY, Allen SG: Efficacy of cyclophosphamide in toxic epidermal necrolysis. *J Am Acad Dermatol* 25:778–786, 1991
9. Villada G, Roujeau JC, Clerici T, Bourgault I, Revuz J: Immunopathology of toxic epidermal necrolysis. *Arch Dermatol* 128:50–53, 1992
10. Osawa J, Kitamura K, Saito S, Ikezawa Z, Nakajima H: Immunohistochemical study of graft-versus-host reaction (GVHR)-type drug eruptions. *J Dermatol* 21:25–30, 1994
11. Hertl M, Bohlen H, Jugert F, Boecker C, Knaup R, Merk HF: Predominance of epidermal CD8+ T lymphocytes with bullous cutaneous reactions caused by beta-lactam antibiotics. *J Invest Dermatol* 101:794–799, 1993
12. Smoller BR, Luster AD, Krane JF, Krueger J, Gray MH, McNutt NS, Hsu A, Gottlieb AB: Fixed drug eruptions: evidence for a cytokine-mediated process. *J Cutan Pathol* 18:13–19, 1991
13. Hindsén M, Christensen OB, Gruic V, Löfberg H: Fixed drug eruption: an immunohistochemical investigation of the acute and healing phase. *Br J Dermatol* 116:351–360, 1987
14. Shiohara T, Nickoloff BJ, Sagawa Y, Gomi T, Nagashima M: Fixed drug eruption. Expression of epidermal keratinocyte intercellular adhesion molecule-1 (ICAM-1). *Arch Dermatol* 125:1371–1376, 1989
15. Hertl M, Schneider R, Merk HF: In vitro-lymphocyte responses to beta-lactam antibiotics in penicillin allergy: cross-reactivity between penicillins and cephalosporins. *Dermatosen* 40:102–107, 1992
16. Roujeau JC, Albengres E, Moritz S, et al: Lymphocyte transformation test in drug-induced toxic epidermal necrolysis. *Int Arch Allergy Appl Immunol* 78:22–24, 1985
17. Koponen M, Pichler W, de Weck AL: T cell reactivity to penicillin: phenotypic analysis of in vitro activated cell subsets. *J Allergy Clin Immunol* 78:645–652, 1986
18. Stejskal VDM, Forsbeck M, Olin R: Side chain-specific lymphocyte responses in workers with occupational allergy induced by penicillins. *Int Arch Allergy Appl Immunol* 82:461–464, 1987
19. Hertl M, Geisel J, Boecker C, Merk HF: Selective generation of CD8+ T cell clones from the peripheral blood of patients with cutaneous reactions to beta-lactam antibiotics. *Br J Dermatol* 128:619–626, 1993
20. Kemey DM, Noble A, Holmes BJ, Diaz-Sachez D: Immune regulation: a new role for the CD8+ T cell. *Immunol Today* 15:107–110, 1994
21. Steinmueller D, Tyler JD, Snider ME, Noble RL, Riser BL, Massab HF, Galli SJ: Tissue destruction resulting from the interaction of cytotoxic T cells and their targets. *Ann NY Acad Sci* 532:106–112, 1989
22. Prinz JC, Groß B, Vollmer S, Trommler P, Strobel I, Meurer M, Plewig G: T cell clones from psoriasis skin lesions can promote keratinocyte proliferation in vitro via secreted products. *Eur J Immunol* 24:593–598, 1994
23. Gaschet J, Mahe B, Milpied N, Devilder MC, Dreno B, Bignon JD, Davodeau F, Hallet MM, Bonneville M, Vie H: Specificity of T cell invading the skin during acute graft-vs.host-disease after semiallogeneic bone marrow transplantation. *J Clin Invest* 91:12–20, 1993
24. Gocinski BL, Tigelaar RE: Roles of CD4+ and CD8+ T cells in murine contact sensitivity revealed by in vitro monoclonal antibody depletion. *J Immunol* 144:4121–4128, 1990
25. Kalish RS, Johnson KL: Enrichment and function of urushiol-specific T-lymphocytes in lesions of allergic contact dermatitis to urushiol. *J Immunol* 145:3706–3709, 1990
26. Dustin ML, Singer KH, Tuck DT, Springer TA: Adhesion of T lymphoblasts to epidermal keratinocytes is regulated by intercellular adhesion molecule 1 (ICAM-1). *J Exp Med* 167:1323–1332, 1988
27. Nickoloff BJ: Role of gamma interferon in cutaneous trafficking of lymphocytes with emphasis on molecular and cellular adhesion events. *Arch Dermatol* 124:1835–1843, 1988
28. Leneis RE, Buchsbaum M, Whitacker D, Murphy GE: Intercellular adhesion molecule expression in the evolving human cutaneous delayed hypersensitivity reaction. *J Invest Dermatol* 93:672–677, 1989
29. Makgoba MW, Sanders ME, Ginther Luce GE, Dustin ML, Springer TA, Shaw SF: Functional evidence that intercellular adhesion molecule 1 (ICAM-1) is a ligand for LFA-1 dependent adhesion in T cell-mediated cytotoxicity. *Eur J Immunol* 18:637–640, 1988
30. Foster CA, Yokozeki H, Rappersberger K, Koning F, Volc-Platzer B, Rieger A, Coligan JE, Wolff K, Stingl G: Human epidermal T cells predominantly belong to the lineage expressing α/β T cell receptor. *J Exp Med* 171:997–1002, 1990
31. Shear NH, Spielberg SP: Anticonvulsant hypersensitivity syndrome: in vitro assessment of risk. *J Clin Invest* 82:1826–1832, 1988
32. Scerri L, Shall L, Zaki I: Carbamazepine-induced anticonvulsant hypersensitivity syndrome—pathogenic and diagnostic considerations. *Clin Exp Dermatol* 18: 540–542, 1993
33. Cribb AE, Spielberg SP: Sulfamethoxazole is metabolized to the hydroxylamine in humans. *Clin Pharmacol Ther* 31:522–526, 1992
34. Hertl M, Jugert F, Merk HF: CD8+ dermal T cells from a sulfamethoxazole-induced bullous exanthem proliferate in response to drug-modified liver microsomes. *Br J Dermatol* 132:215–220, 1995
35. Riley RJ, Smith G, Wolf CR, Cook VA, Leeder VS: Human anti-endoplasmic reticulum autoantibodies produced in aromatic anticonvulsant hypersensitivity reactions recognize rodent CYP3A proteins and a similarly regulated human P450 enzyme(s). *Biochem Biophys Res Commun* 91:32–40, 1993
36. Kalish RS, LaPorte A, Wood JA, Johnson KL: Sulfonamide-reactive lymphocytes detected at very low frequency in the peripheral blood of patients with drug-induced eruptions. *J Allergy Clin Immunol* 94:465–472, 1994
37. Niederau D, Fritzsche R, Merk H: Lymphocyte transformation test with drug-modified microsomes. *Z Hautkr* 68:581–585, 1993
38. Bryunzeel DP, von Blomberg-van der Flier M, Scheper J, van Ketel WG, de Haan P: Penicillin allergy and the relevance of epicutaneous tests. *Dermatologica* 171:429–434, 1985
39. Harle DG, Baldo BA: Identification of penicillin allergenic determinants that bind IgE antibodies in the sera of subjects with penicillin allergy. *Mol Immunol* 27:1063–1071, 1990
40. Lafaye P, Lapresle C: Fixation of penicilloyl groups to albumin and appearance of anti-penicilloyl-antibodies in penicillin-treated patients. *J Clin Invest* 82:7–12, 1988
41. Scherzer W, Kraft D, Cerni C, Scheiner O, Lackner J, Spitzy KH: Aminopenicillin Exantheme—eine multizentrische, prospektive Studie. *Dermatosen* 28: 175–181, 1980
42. Blanca M, Perez E, Garcia J, Miranda A, Fernandez J, Vega JM, Terrados S, Avila M, Martin A, Suau R: Anaphylaxis to amoxycillin but good tolerance for benzylpenicillin. *Allergy* 43:508–510, 1988
43. Kalish RS, Wood JA, LaPorte A: Processing of urushiol (poison ivy) hapten by both endogenous and exogenous pathways for presentation of T cells in vitro. *J Clin Invest* 93:2039–2047, 1994
44. Bell SJ, Pichler WJ: Penicillin-allergic patients react to penicillin-modified "self". *Allergy* 44:199–203, 1989
45. Romagnoli P, Spines GA, Sinigaglia F: Gold-specific T-cells in rheumatoid arthritis patients treated with gold. *J Clin Invest* 89:254–258, 1991
46. Claas FHJ, Rumia-van Nieuwkoop R, van den Berge W, van Rood JJ: Interaction of penicillin with HLA-A and B antigens. *Hum Immunol* 5:83–90, 1982
47. Mobini N, Ahmed AR: Immunogenetics of drug-induced bullous diseases. *Clin Dermatol* 11:449–460, 1993