

Review article

Pathogenesis of drug-induced exanthems

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Drug allergy is a common problem in daily practice (1, 2). However, the lack of understanding of its physiopathology, the lack of animal models, the wide variety of clinical features, and the abundance of potential elicitors, make it a difficult and somewhat neglected field in medical research. Nevertheless, allergologists often see certain clinical features that may represent a drug allergy, and will want to know which drug might be responsible for a presumed drug allergy. Yet there are only limited possibilities to determine this, for as long as the pathomechanisms of different types of drug allergy are not clarified, since diagnostic procedures relate to the type of immune mechanism.

The most frequent drug reactions are different forms of exanthems. Some appear rapidly after drug intake, e.g. immediate-type reactions like urticaria and angioedema. Others appear hours or days after drug intake; they are the so-called delayed-type reactions, comprising a broad spectrum of clinical and distinct histopathological features. They manifest themselves as maculopapular, bullous and even pustular exanthema.

In recent years immunohistological studies of skin lesions, as well as the generation and analysis of drug-specific T-cell lines (TCL) and T-cell clones (TCC) from

allergic patients, suggested that drug-specific T cells play a major role in these drug-induced skin reactions (3–5). These studies have revealed that distinct functions of T cells can be associated with different clinical pictures of drug allergies (6–15). This review presents these developments and their impact on the understanding of three distinct drug-induced side-effects, namely maculopapular exanthema (MPE; which represents the most commonly encountered cutaneous adverse drug reaction), bullous, and pustular skin reactions.

Drug recognition by T cells: role of drug presentation and danger hypothesis

T cells recognize antigens in the form of small peptides presented by major histocompatibility molecules like MHC class I or II. Like other small chemicals (generally <1000 D) drugs can be immunogenic by three mechanism (Figs 1 and 2):

1) they are chemically reactive and bind like haptens to larger cell-bound or soluble molecules, i.e. penicillins or cephalosporins (16)

2) other compounds are not chemically reactive but are metabolized to a reactive compound, the “prohappen” concept (17)

3) newer data from our group shows that a third possibility exists, namely a pharmacological interaction with immune receptors, the “p-i-concept” (15, 18). Drugs associate in a rather labile, noncovalent way with the MHC-peptide complex. This labile binding is, however, sufficient to stimulate T cells which bear a

Abbreviations: ADR: adverse drug reaction; AGEF: acute, generalized exanthematous pustulosis; APC: antigen presenting cells; CTL: cytotoxic T lymphocytes; IFN: interferon; LTT: lymphocyte transformation test; MPE: maculopapular drug eruption; PMN: polymorphonuclear (neutrophilic) leukocyte; SMX: sulfamethoxazole; TCC: T cell clones; TCL: T cell lines; TEN: toxic epidermal necrolysis.

“fitting” T-cell receptor (TCR) for the antigen (drug). Thereby the additional, sandwich-like interaction of the drug with the TCR may stabilize the binding and thus allow intracellular signaling (Figs 1 and 2).

Patients develop drug reactions after a sensitization phase, which lasts normally >3–4 days, frequently even longer. We do not yet understand how the sensitization occurs. This primary sensitization is likely to happen in the lymph nodes. It requires three factors:

- 1) covalent binding to a protein, which is processed and presents the modified peptide on MHC molecules; alternatively, the drug can bind directly to the MHC–peptide complex

- 2) the availability of T cells able to react with the compound be it presented by covalent or noncovalent binding

- 3) an additional “danger” signal which indicates to the immune system to react (19, 20).

The latter is normally activating the antigen(drug)-presenting cell (APC), e.g. by interacting with Toll-like receptors and leads to the up-regulation of adhesion molecules, improved interaction with T cells and enhanced cytokine production by the APC (20). If this danger signal is not provided, the immune system ignores the drug presentation, which appears to be the predominant type of immune response to drugs.

Enhancing (danger) factors seem to be provided in the frame of a generalized, massive immune stimulation as it occurs during HIV or acute EBV/HHV-6 infections as well as during acute exacerbations of autoimmune diseases like Sjögren’s syndrome or SLE. In these viral and autoimmune diseases drug allergies occur far more frequently (21–23).

We proposed that this hyperreactivity may arise from the lowered threshold of immune reactivity in such situations of massive immune activation, the abundantly available co-stimulatory molecules and cytokines, as well as the better presentation of drugs by activated (professional and nonprofessional) APC (24). Danger might also be provided by some drug metabolites themselves, namely if a metabolite is generated that has a toxic effect on the cell and thereby also provides an inflammatory signal, which boosts the immune response. For example, if a drug damages kidney cells then the manifestation of the drug allergy might also occur in this organ, as the damage might lead to a local “danger” signal (20–24).

The danger hypothesis may also explain the preferential localization of drug allergies in the skin (24). The skin is a border region where the immune system constantly faces new challenges. It may therefore have a high propensity to react to many antigens, which could lower the threshold of immune reactivity to some rather innocuous antigens as well. In contrast, in the gastrointestinal tract, tolerance may dominate.

The kind of drug binding to the presenting molecule (covalent or noncovalent) also has an impact on the

type of immune reaction that evolves, and might thus contribute to distinct clinical pictures in drug allergy (25). Drugs acting as haptens can modify MHC molecules themselves, or the embedded peptides; they can alter different proteins, be they soluble or on cells (25). Therefore, hapten-like drugs are able to elicit all types of drug-related immune reactions, from antibody-mediated diseases like anaphylaxis and hemolytic anaemia to various T-cell mediated reactions like maculopapular drug eruption (MPE), acute generalized exanthematous pustulosis (AGEP), Stevens–Johnson syndrome, etc.

Other drugs are also notorious for eliciting allergic side-effects, but the clinical picture is more limited: carbamazepine seems to elicit MPE and drug-hypersensitivity syndromes but not anaphylaxis. For T-cell mediated reactions, labile binding to MHC molecules might be sufficient to trigger an immune response. Moreover, the binding of some drugs to MHC molecules is probably the only way to acquire immunogenicity: e.g. carbamazepine-elicited reactions are exclusively T-cell mediated, possibly because the molecule is presented to the immune system solely by its ability to bind to MHC–peptide complexes (Fig. 2).

Both reactions due to hapten-binding or to labile, noncovalent presentation might occur simultaneously. For example, sulfamethoxazole (SMX) may cause the majority of exanthematous skin reactions due to labile binding, while the hapten like metabolite sulfamethoxazole nitroso (SMX-NO) might be responsible for IgE-mediated reactions in SMX allergy.

Histology of exanthem

In electron microscopy, the primary changes of maculopapular drug eruptions (MPE) are intercellular and intracellular edema as well as disruption of epidermal basal cells, which show pyknotic nuclei (Fig. 3) (26–31). A vacuolar alteration of keratinocytes at the basal cell layer is often seen, as well as some scattered individual dyskeratotic and necrotic keratinocytes (26–29) (Fig. 3). In immunohistology an interface dermatitis is frequently present with superficial, mainly perivascular, mild to moderate mononuclear cell infiltrate. It is composed of CD3⁺ T cells with a predominance of CD4⁺ T cells in the perivascular dermis, whereas both CD4⁺ and CD8⁺ T cells, mostly in equal numbers, are located at the dermoepidermal junction zone and in the epidermis. In addition, some eosinophils are found in the dermis (5, 28–31).

As a marker of cell activation, CD25 (α -chain of the IL-2 receptor) is detected in up to 15% of the T-cell infiltrate, especially on those located at the dermoepidermal junction zone. Ninety to 100% of the mononuclear cell infiltrate is strongly positive for the human

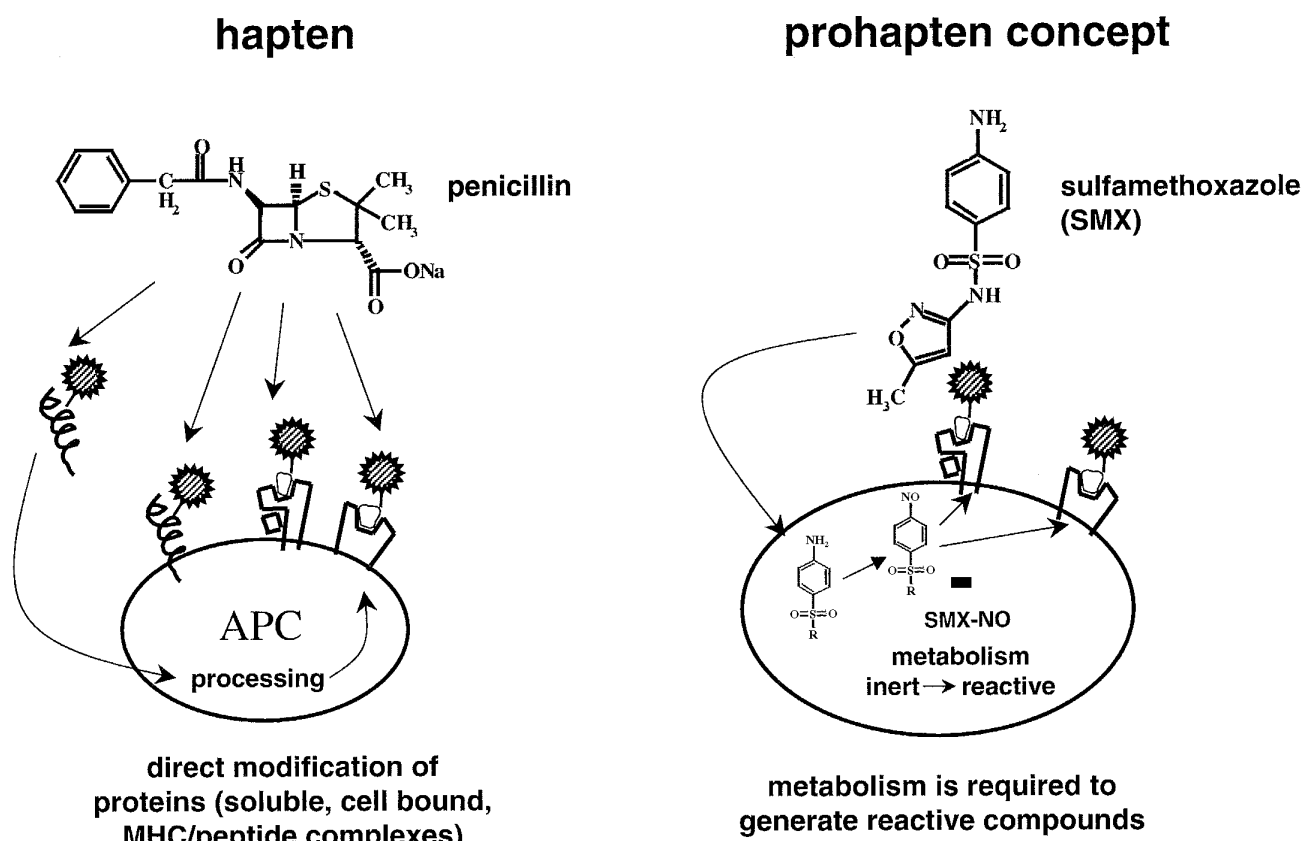


Figure 1. Hapten and prohaptent concepts. Hapten-like drugs like penicillins can bind covalently to molecules, whether cell-bound or soluble, or even to the immunogenic peptide–MHC molecule itself. Other drugs are “prohaptens”; that is they require metabolism to become chemically reactive haptens. The metabolism occurs mainly inside cells and may lead to modification of cell-bound or soluble proteins. Both reactions can lead to B-cell and T-cell mediated immune responses.

leukocyte antigen HLA-DR (29). The infiltrating T cells also express adhesion molecules like LFA-1 (CD11a–CD18) and L-selectin (CD62L) (29, 30). Among the resident T cells endothelial cells are activated, and they express various adhesion molecules such as E-selectin (CD62E), P-selectin (CD62P), adhesion molecules PECAM-1 (CD31) and ICAM-1 (CD54) (30, 31). Interestingly, in MPE (but *not* in AGEP) keratinocytes are stimulated and express MHC class II (5, 28) and are therefore potentially able to present antigens to CD4⁺ T cells. CD56⁺ natural killer (NK) cells are only present on up to 6% of the cell infiltrate in MPE (29).

Some of these events in the skin are also mirrored in peripheral blood. During acute drug-allergic skin reactions, the skin homing receptor CLA⁺ is elevated on circulating T cells and it disappears after remission (32). Circulating T cells also express transiently variable activation markers like HLA-DR (5). Interestingly, more CD8 than CD4 cells are activated, in spite of a dominant CD4 cell presence in the affected skin (5).

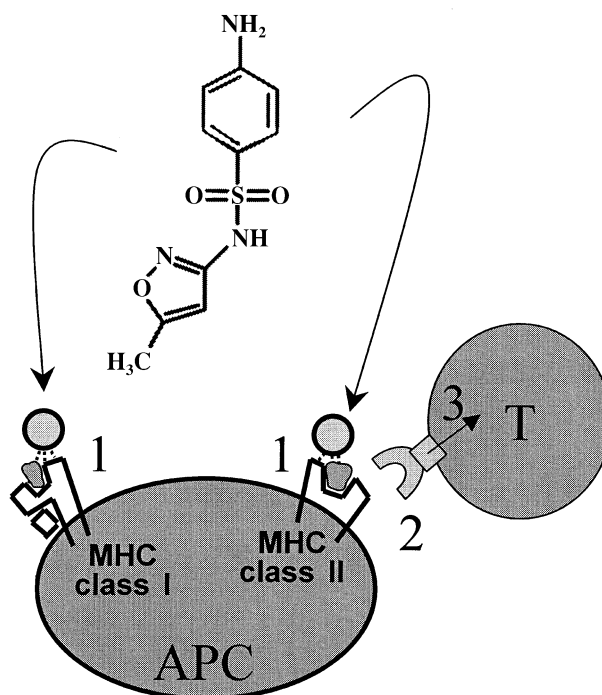
Killer cells in exanthems

What is causing the death of the keratinocytes? Up to

20% of the infiltrating T cells in drug-induced maculopapular exanthema express perforin and granzyme B (29), which are important mediators of cell-mediated cytotoxic reactions (33). These cytotoxic granule proteins trigger cell death by forming pores in the target cell membrane and inducing degradation of their DNA. Interestingly, perforin- and granzyme B-positive cells are often located at the dermoepidermal junction zone or in the epidermis, along with signs of keratinocyte cell damage. Double immunostaining for cytotoxic molecules and CD4 or CD8 indicate that both cell types may have cytotoxic potential (5, 29). These results are further substantiated by the presence of perforin containing CD4⁺ (and CD8⁺) T cells in the blood of patients with drug eruptions (29, 34), in cells eluted from positive patch test reactions after drug allergy (35), and by the finding that drug specific T-cell clones killed drug-presenting autologous keratinocytes *in vitro* (10).

The immunohistology of rather mild bullous skin diseases is actually quite similar to MPE: massive T-cell infiltration, MHC up-regulation on keratinocytes and immigrating T cells, and IL-5 expression in the lesions (5, 29, 51); with the decisive difference that more CD8⁺ T cells are involved, and bullae are formed (5).

non hapten
(non-covalent binding,
direct drug presentation)



**labile binding of drugs to
MHC/peptide complexes**

Figure 2. Noncovalent association of the drug with MHC–peptide complexes triggers T cells with fitting T-cell receptors (TCR), causing drug-induced stimulation of T cells. The p-i-concept (pharmacological interaction with immunological receptors) has been shown for sulfamethoxazole, lidocaine/lignocaine, mepivacaine, and celecoxib, and leads to exclusive T cell reactions. 1) the chemically inert drug binds in a labile way to MHC–peptide complexes (MHC class I or II); 2) T cells screen the MHC molecules and if a TCR fits into the drug–MHC–peptide complex, it is binding and receives a signal; 3) the signal is interpreted as immunological as the responsive cell is a T cell.

These CD8⁺ T cells are killer cells. Hertl et al. showed that in amoxicillin-induced bullous skin reactions, CD8 cells eluted from the skin could kill other cells after mitogen stimulation (4, 11). They might be more damaging than CD4⁺ killer T cells, as they have the potential to kill not only MHC class II-expressing cells, but also the majority of MHC class I-bearing cells. This concept has been confirmed recently by analysis of perforin, granzyme B, TNF- α and FasL in different forms of drug-elicited exanthema, as higher levels of perforin and granzyme were found in the more severe, bullous drug-induced diseases (36).

It is well established that cytotoxic T lymphocytes (CTL) may mediate cytotoxicity not only by perforin/granzyme B but also via death receptors like Fas/Fas ligand (FasL). FasL differs from perforin-mediated killing, as no direct cell contact is required: the released FasL may kill innocent bystander cells if they express

Fas-receptors and are somehow crosslinked. This mechanism could thus explain the death of cells distant to the infiltrating T cells, or the fulminate killing of many cells in spite of the absence of cell infiltration, as it is typical in toxic epidermal necrolysis (TEN).

Recent evidence has implicated a role for these molecules in the pathogenesis of TEN (37). It was also confirmed by the analysis of FasL expression in the circulation of patients with acute drug-induced exanthema. Only patients with TEN had detectable FasL mRNA levels, as measured by quantitative polymerase chain reaction (36). On the other hand, analysis of drug specific T-cell clones and T-cell lines from patients with rather mild exanthems can also show FasL-mediated killing (Kuechler P et al. in preparation).

The most severe forms of bullous skin diseases are Stevens–Johnson syndrome and TEN. A recent study of

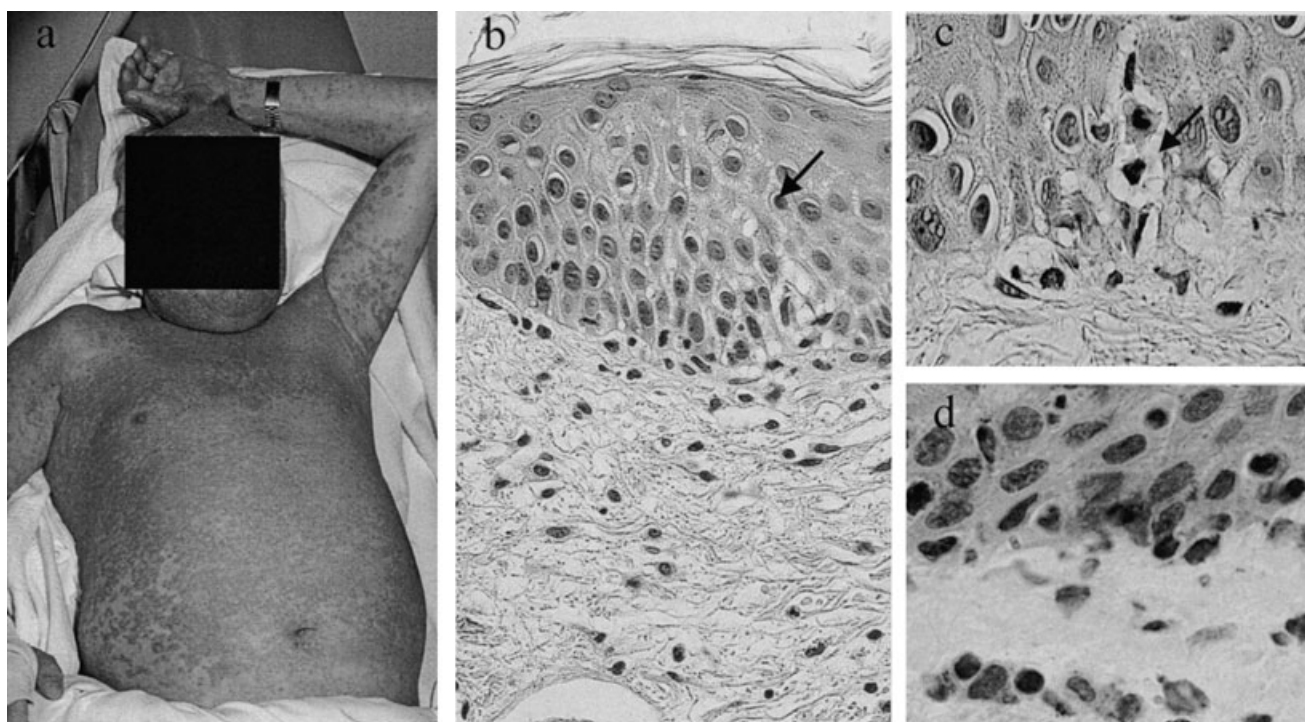


Figure 3. Clinic appearance and histology of acute maculopapular drug eruption (MPE). The typical changes observed in histology comprise hydropic degeneration of keratinocytes (b); necrosis of keratinocytes (b, c); infiltration of perforin- and granzyme B-positive T cells into the epidermis (d).

the cells within bullae of patients with TEN revealed $CD8^+$ T cells with some NK-like features and cytotoxic capacity during the initial phase, while later in the disease monocytes were present (38, 39). These cytotoxic $CD8^+$ T cells are $TCR-\alpha\beta^+$, express partly $CD56^+$ and kill via perforin/granzyme B. Interestingly enough, these T cells recognize the inert parent compound SMX (39), supporting the relevance of noncovalent drug binding even in this most severe form of cutaneous drug allergy.

Cytokines in maculopapular exanthem

Drug-specific T cells may also orchestrate skin inflammation through the release and induction of different cytokines and chemokines. In contrast to most peptide specific T-cell responses, where either a Th1 or Th2 cytokine pattern can be found, analysis of various drug-specific TCC *in vitro* has revealed that these cells show a heterogeneous cytokine profile, including type 1 and type 2 cytokines (7, 12, 13), while one group found a more Th2 like pattern (40).

A moderately and strongly enhanced expression in skin lesions for interferon(IFN)- γ and IL-5, respectively, is in accordance with such a heterogeneous cytokine pattern (28). Thus, two clearly distinct immune reactions might occur simultaneously, as the $CD8^+$ T-killer cells found in bullous skin diseases secrete high levels of IFN- γ , while the $CD4^+$ T cells secrete IL-5 (28).

The enhanced expression of IL-5, a key factor in regulating the growth, differentiation and activation of eosinophils, is of particular relevance as eosinophils are frequently increased in these reactions. Indeed, some patients with MPE show high IL-5 levels in the serum during the acute stage (41, 42), and some drug-specific TCC produce a very high level of IL-5 upon specific or unspecific stimulation (43).

Subclassification of type IV reactions according to distinct effector cell usage

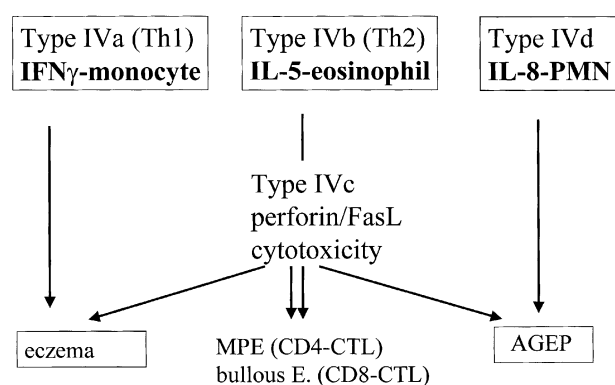


Figure 4. Type IV reactions can be related to distinct T-cell mediated immune functions with the recruitment of distinct effector cells. These reactions can be subclassified as IVa, IVb, IVc and IVd. Frequently, these reactions occur together. The clinical picture is due to the dominant T cell function and effector cell involvement.

Table 1. Danger signs in drug induced exanthema

Clinic	Laboratory
Extent of exanthema	
Extent of infiltration	Differential blood count*
Formation of bullae/pustules	Eosinophilia
Nikolsky sign positive, painful skin	Presence of atypical (activated) lymphocytes in the circulation
Involvement of mucous membranes	Alanin and Aspartate aminotransferase (increase > × 2)
Systemic symptoms	
Fever, lymphadenopathy	C-reactive protein *
	Corresponding analyses according to clinical signs (urinalysis, creatinine, etc)
Liver, kidney, lung, pancreas involvement	

* Should always be done in acute severe maculopapular drug eruption (MPE) and all more severe exanthems such as bullous exanthema or acute, generalized exanthematous pustulosis (AGEP).

Immunohistochemical analysis of different chemokines in MPE has revealed a strong expression of eotaxin and RANTES protein and, to a lesser degree, MCP-3 and IL-8 (28). Besides IL-5, eotaxin has been reported to have major effects, particularly on the recruitment and activation of eosinophils, and accumulating evidence indicates cooperation between eotaxin and IL-5 in inducing optimal maturation, activation and recruitment of eosinophils. Eotaxin was also found to be expressed by drug-specific T-cell clones (44). In addition to T cells, eosinophils may contribute to the generation of tissue damage by the release of various toxic granule proteins, such as eosinophilic cationic protein, major basic protein, and eosinophil peroxidase; they may also be involved thereby in amplifying the underlying immune response in drug-induced maculopapular exanthema.

A peculiar drug-induced skin reaction of model character for T cell–neutrophil interaction is acute generalized exanthematous pustulosis (AGEP). This disease is caused by drugs in >90% of cases; its clinical hallmarks are many (>100) disseminated sterile pustules; patients have fever and massive leukocytosis in the blood, sometimes with eosinophilia (45, 46). The involvement of T cells has been suggested by a frequently positive patch test reaction to the incriminated drug (47) which, interestingly, imitates the morphology of the original reaction, sometimes even with pustule formation (8).

Immunohistology of acute lesions typically revealed the presence of intraepidermal pustules, which were filled by neutrophilic leukocytes (PMN) and surrounded by activated HLA-DR-expressing CD4⁺ and CD8⁺ T cells (8). In contrast to MPE and bullous skin reactions, the keratinocytes did not express MHC class II, but showed an elevated expression of the neutrophil-attracting chemokine IL-8 (CXCL-8). Surprisingly, even the T cells emigrating into the epidermis expressed IL-8. The *in vitro* analysis of drug-specific T-cell clones obtained from the blood or patch test lesions confirmed the high IL-8 production of these cells, while patients with other drug reactions had no IL-8 production. Thus, this drug-induced disease might represent a

model for T cell–PMN interaction (8). This interaction is widely neglected in clinical and immunological research, but might be important in various diseases where T cells and neutrophils appear to cooperate, for example as in psoriasis, reactive arthritis or Behçet's disease.

Subclassification of type IV reactions based on effector cell recruitment

Drug allergies are typical examples of diseases that can be subclassified into four categories by the Coombs and Gell classification (48). Type I are due to IgE-mediated reactions, mainly causing urticaria, anaphylaxis and asthma; type II correspond to immunoglobulin-mediated cytotoxic mechanisms, accounting mainly for blood cell dyscrasias; type III reactions are immune complex-mediated (e.g. vasculitis); and type IV are T-cell mediated reactions causing so-called delayed hypersensitivity reactions.

This classification helps to correlate the clinical symptoms to the underlying immune mechanism and is of proven help in clinical practice. The term “delayed hypersensitivity reaction” was originally coined to describe T cell reactions to tuberculin, but the term became more and more imprecise as new insights into T cell biology revealed great heterogeneity of T cell functions, leading to quite distinct clinical features that differ from a tuberculin reaction. Indeed, more recently published textbooks of immunology have tried to incorporate the modern concepts of T cell biology and heterogeneity. They have subdivided type IV delayed-hypersensitivity reactions according to production of distinct cytokines: Th1 for type IVa, Th2 for type IVb, and cytotoxic T cells for type IVc (49). On the other hand, in clinical terms the involvement of distinct effector cells may be more relevant than cytokine production by the T cell, frequently overlapping in the distinct clinical manifestations of drug allergy. For instance, elevated production of IL-5 and IFN- γ is found in MPE, bullous exanthema and AGEP, which are quite clinically distinct diseases.

If T cell function leads to monocyte/macrophage activation, it is called a type IVa reaction. This immune response probably best correlates to a Th1 reaction leading to a delayed-type reaction, as in a tuberculin skin test. It is distinct from a predominantly eosinophilic inflammation, which is due to a vigorous Th2 response with high IL-5 production (type IVb). T-cell mediated cytotoxicity (by CD4 and CD8⁺ T cells) is an important function in various immune reactions and in particular for most drug-induced exanthems (type IVc reactions); and the T-cell regulated, sterile, PMN-rich pustule formation can be traced to high IL-8 production by T cells, which can be termed a type IVd reaction (Fig. 4).

It must be emphasized, however, that most drug allergies (possibly other immune responses as well) represent overlapping immune reactions, where various T cells with distinct functions contribute to the clinical picture. The clinical picture is due to the dominant T cell function and subsequent characteristic effector cell recruitment but detailed analysis frequently reveals overlapping functions. In all exanthems, CTL of either the CD4 or CD8 phenotype appear to be involved, sometimes with additional recruitment of eosinophils, sometimes of PMN. Patients with AGEP not only have enhanced PMN in blood and tissue, but also (frequently) eosinophilia (8). Similarly, patients with bullous skin disease might not only have high activation of IFN- γ -producing, cytotoxic CD8⁺ T cells, but also eosinophilia due to IL-5-producing CD4⁺ T cells.

Diagnosis of drug allergy

The diagnosis of drug allergy is based on an exact history, clinical examination and some laboratory and skin tests. While some clinical symptoms, like exanthem, are quite characteristic, other drug allergies are difficult to recognize as such and might be missed. The severity of a drug allergy depends on the strength and type of the immune reaction (IgE-mediated or not; CD8-cell stimulation or not), and the involved organs. While a mild rash is in most instances harmless and transient, certain danger signals can point to a more severe course. These include certain laboratory parameters such as elevated liver enzymes, the presence of activated lymphocytes, and a high eosinophilia in the circulation (Table 1).

Identification of the relevant drug can be made by skin tests, serology, and cellular *in vitro* tests; tests that mimic the pathogenetic events of the original reaction are more relevant. The detection of drug-specific IgE by skin or laboratory tests in patients with drug-induced anaphylaxis is an ominous sign. Moreover, it can be convincing to see a dermatitis-like reaction after a patch (epicutaneous) test in a patient with contact dermatitis. However, only some of these tests are available and standardized for a small spectrum of drug reactions.

As drug-specific T cells orchestrate all types of immune reactions, and cytotoxic T cells themselves are involved in certain drug-induced pathologies, it is logical to define the relevant drug by detecting sensitized T cells in these reactions. There are two types of tests available: skin tests (patch tests, occasionally late reading of intradermal tests) and *in vitro* tests. There are obvious difficulties with these tests, so leaving the field of drug allergy diagnosis open to further clinical research. There is an enormous heterogeneity of possible elicitors; the compound might be difficult to identify; the reaction might be directed to a metabolite or to an additive of the drug; or the manufacturer might not provide the pure substance. Validation needs the tests to be standardized in well-defined patients, where possible provoked by the drug. For many drugs this goal cannot be achieved in a realistic time-frame.

With regard to skin tests, one must consider the ability of the drug to penetrate the skin and that it may be irritative in some individuals. Moreover, delayed skin tests (epicutaneous or patch) are considered positive if an inflammatory response develops in the skin (50–52), a response which not all drug-specific T cells are able to elicit to the same degree (Th2 < Th1). Indeed, the sensitivity of patch tests depends on the type of clinical reaction. Patients with AGEP frequently have positive test results (47), while patients with MPE have positive test results less frequently (40–60%) (5), and patients with IgE-mediated allergy rarely test negative although they harbour drug-specific T cells (53). In general, a positive test result is helpful, but a negative one cannot exclude a drug allergy.

There is, however, some promising progress. Elution of T cells from patch test lesions reveal that about 30% are drug-specific (54). One of the most frequent drug allergies, MPE to amoxicillin, can be detected quite reliably by patch and intradermal tests (52). Furthermore, patch-testing to other compounds is becoming better standardized (54–56).

The lymphocyte transformation test (LTT) measures the proliferative response of T cells to the drug under optimal *in-vitro* conditions (57–63). LTT requires living cells; the anticoagulated blood should be handled within 24–36 h. The test is rather cumbersome, taking about 1 week, as it relies on measuring the proliferation of drug-specific T cells in a cell culture system with various variables (composition of circulating and isolated mononuclear cells, availability of optimal serum supplements for the cell culture, etc.). Some groups have had good experiences with LTT, with a sensitivity of 58–78% and specificity of 85–100% (5, 57, 61, 62), but other groups have found it less useful (63). The description of metabolism-independent drug recognition by T cells (15, 18) and the detection of drug-specific TCC in the circulation of drug-allergic individuals (6–11, 13, 15) confirms the principles and

feasibility of this test. LTT can be positive with a variety of drugs in MPE, bullous disorders, AGEP, drug hypersensitivity syndrome, isolated hepatitis, pancreatitis, nephritis (particularly if accompanied by eosinophilia), and even in patients with IgE-mediated allergy (anaphylaxis, urticaria) (56). Yet it is frequently negative in patients with TEN, fixed drug eruptions, and vasculitis (63).

The advantages of LTT are that as an *in vitro* test it is not dangerous, that it is able to detect different forms of T cell reactions (64), and that it offers the possibility to better characterize the T-cell response *in vitro*, i.e. by measuring cytokines (7, 58, 64). The main disadvantage is a lack of standardization very difficult to achieve with a cellular test that relies on proliferation and has 71,000 different antigens and its complicated nature, namely that live cells are required. Moreover, it is difficult to interpret the clinical meaning of *in vitro* T-cell proliferation and its relation to a certain clinical disease. And, as with other immunological tests, the detection of sensitization may not necessarily mean that a pathology will develop again with re-exposure to the drug.

Conclusions

Hypersensitivity reactions to drugs can cause a variety of skin diseases like maculopapular, bullous and pustular eruptions. Understanding the underlying pathological mechanisms teaches much about immune reactions in general, and may help understanding of diseases which are imitated by drug allergies. Drugs can be recognized by $\alpha\beta$ -T cell receptors not only if bound covalently to peptides, but also if the drug binds in a rather labile way to the presenting MHC-peptide complex, and this presentation is sufficient to stimulate T cells. Immunohistochemical studies of exanthems

demonstrate the presence of cytotoxic CD4⁺, and to a lesser degree CD8⁺ T cells, which contain perforin and granzyme B. They are close to keratinocytes that show signs of cell destruction. Patients with bullous skin disease show strong CD8⁺ T cell emigration to the epidermis, probably due to preferential presentation of the drug by MHC class I molecules. Drug-specific T cells also orchestrate inflammatory skin reactions through the release and induction of various cytokines (i.e. IL-5, IL-6, TNF- α , IFN- γ), and chemokines (i.e. RANTES, eotaxin or IL-8). The high level of IL-5 may contribute to the generation of tissue and blood eosinophilia, a typical hallmark of many drug allergic reactions. While in a peculiar form of drug allergy, so-called acute generalized exanthematous pustulosis (AGEP), high levels of IL-8 may cause recruitment of neutrophils, which are the predominant cells within pustules.

Based on clinical and immunological data on different forms of drug allergy, they can be subclassified beyond the usual classification of IgE-mediated and non-IgE-mediated drug allergies (65). T-cell mediated delayed type IV reactions can be classified as type IVa (Th1-like), IVb (Th2-like), IVc (cytotoxic), and type IVd (T-cell reactions leading to neutrophilic inflammation). Quite frequently, distinct functions of T cells occur together leading to a heterogeneous clinical picture. Diagnosis of these drug allergies should rely on test procedures that detect sensitized T cells, however the respective tests need to be better standardized.

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