

STATE OF THE ART REVIEWS ON MECHANISMS OF ALLERGIC DISEASE

Pathogenesis of drug allergy – current concepts and recent insights

B. Schnyder¹ and K. Brockow²

¹Clinic for Rheumatology and Clinical Immunology / Allergology, Inselspital, Bern, Switzerland and ²Department of Dermatology and Allergology Biederstein, Technische Universität München, Munich, Germany

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Summary

Drug hypersensitivity reactions (DHRs) may be caused by immunologic and non-immunologic mechanisms. According to the World Allergy Organization, drug allergy (DA) encompasses the subgroup of immunologic DHRs which are mediated either by specific antibodies or specific T lymphocytes. Due to the immunologic memory, DA reactions bear an increased risk for dramatically enhanced reactions on re-exposure. Some current concepts of DA were described decades ago. Drug allergies to soluble macromolecular protein drugs such as biopharmaceuticals are predominantly T cell-dependent drug-specific antibody responses leading to IgE- or IgG-mediated allergy. However, most drugs are too small to be directly recognized by specific B and T cells. Immune reactions to low-molecular drugs have been explained by the hapten model: a hapten drug can bind covalently to soluble autologous proteins (e.g. serum albumin). Resulting compounds may then be recognized by matching B cell receptors (BCRs) and induce a specific T cell-dependent IgE- or IgG-antibody production. Drug haptens may bind to extra- or intracellular proteins, which are processed and presented by various professional antigen-presenting cells (APCs). Depending on the APC, they may induce not only specific antibody production, but also non-immediate T cell-mediated DA. More recently, a supplementary effector mechanism for non-immediate DA to low-molecular drugs has been described, namely the pharmacological interaction of native low-molecular drugs with immune receptors (p-i-concept). Low-molecular drugs may directly and reversibly attach to immune receptors. These non-covalent interactions may modify the affinity between autologous major histocompatibility complex (MHC), presented peptides and specifically primed T cell receptors (TCRs) and thereby stimulate T cells. A special type of p-i-reaction has been recently described between the antiviral drug abacavir and the F pocket of HLA-B*57:01. This interaction causes an alteration of the MHC-presented self-peptide repertoire and may consecutively lead to a kind of auto-reactivity. Such types of reactions can explain the strong MHC-HLA associations which have been found for some T cell-mediated DHRs.

Correspondence: Knut Brockow, Department of Dermatology and Allergology Biederstein, Technische Universität München, Biedersteiner Str. 29, 80802 München, Germany. E-mail: knut.brockow@lrz.tu-muenchen.de.

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Definition of adverse drug reaction and drug allergy

The World Health Organization defines an adverse drug reaction (ADR) as a noxious and unintended response to a drug that occurs at a dose normally used in man [1]. ADRs encompass all unintended adverse events caused by a certain drug regardless of the involved pathogenic mechanism. Different classifications of ADRs exist [1–3]. The currently prevailing classification has been proposed by Rawlins and Thompson [4]. It differentiates two major subtypes (Table 1):

- 1 Type A reactions, which are due to the pharmacological propriety of the causative drug and occur on exposure in most individuals.
- 2 Type B ($\approx$ DHR), which occur only in predisposed individuals and are thus mostly hard to predict.

Before a new drug is authorized for marketing by drug regulatory agencies, it undergoes extensive toxicological and pharmacological trials in animals and humans. These reveal most type A reactions. However, type B reactions ($\approx$ DHRs) are more difficult to detect, particularly if they occur in less than 1 in 1000 patients.

Table 1. Classification of adverse drug reactions (adapted from [4])

Type	Mechanism	Examples
Type A «pharmacologic» all individuals	Toxic «side»-effects	ASS-induced gastritis
Type B Only susceptible individuals	Non-allergic: Altered effects in metabolic variants Dysbalance of mediators Unspecific mast cell degranulation. Allergic: Mediated by the specific immune system	Prolonged neuromuscular blockade in pseudocholinesterase deficiency. ACE inhibitor-induced angioedema. 'Pseudoallergy' to radiocontrast media IgE- or T cell-mediated penicillin hypersensitivity

Type B reactions may be caused by various mechanisms. Individual susceptibility may arise from metabolic variations, or individual conditions such as inflammations, cytokine dysbalance or specific immune reactions. The nomenclature of allergy is a matter of debate. Some immunologists consider only IgE-mediated $\pm$ T cell-mediated immune reactions to be truly allergic, because they are the most prevalent drug reactions and the mechanism is well documented. For the purpose of this review, however, we have followed the terminology proposed by the European Academy of Allergology and Clinical Immunology and World Allergy Organization, which considers all four types of immunologic reactions according to Coombs and Gell as being allergic [5]. According this terminology, drug allergies (DAs) are only those DHRs, which are specific immune responses. They are mediated either by specific antibodies and/or specific T cells. They do not include unspecific immune reactions such as unspecific mast cell histamine release. A characteristic of specific immune reaction is the immunologic memory due to clonal expansion and somatic hypermutation of the involved specific B cells and/or T cells. Thus, allergic reactions bear an increased risk for dramatically enhanced reactions on re-exposure compared with other hypersensitivity reactions. They are dreaded more than other DHRs, and their correct recognition is of clinical relevance.

Allergy to high-molecular protein drugs

Most macromolecular drugs are biopharmaceuticals (biologicals). They are manufactured in biological sources or extracted from them. Most biologicals are protein drugs (e.g. recombinant cytokines, enzymes, fusion proteins and monoclonal antibodies). The typical immune response to such an antigen is a T cell-dependent antibody formation, such as seen in DA on repeated administration of antivenom sera harvested from animals. However, even human recombinant therapeutic proteins can cause specific antibody responses on repeated administration because nearly all these drugs show differences in some three-dimensional protein composition as compared to the patient's own proteins.

Sensitization to high-molecular protein drugs

The mechanism of induction of a T cell-dependent antibody response to protein drugs is equal to the response to other foreign antigenic proteins. It needs a close cooperation of B cells with T helper 2 (Th2) cells and can be described in three steps:

- 1 Biopharmaceuticals distributed in the extracellular space as dissolved proteins may be specifically recognized and bound by compatible BCRs on B cells. Such BCR drug binding can activate concerned B cells, which then express CD80 (B7.1) or CD 86 (B7.2). However, this signal alone is not sufficient to induce B cell proliferation and differentiation. For that to happen, T cell help including CD40L-CD40 interaction is required.
- 2 T cell help needs the presentation of the drug as antigenic peptide on the major histocompatibility complexes (MHCs) class II of professional antigen-presenting cells (APCs), which can activate naïve T helper (Th) cells bearing T cell receptors (TCRs) with appropriate specificity. The most efficient APC for the presentation of protein drugs are presumably follicular B cells in lymphoid follicles bearing compatible BCR. They are able to specifically bind, internalize and process the soluble drug and to present it as an antigenic peptide on their MHC II molecules. After activation, follicular B cell can migrate to the T cell zone where they encounter naïve Th and provide them necessary costimulatory signals such as the B7 molecule for T cell differentiation towards Th2 (Fig. 1).
- 3 Close contact of drug peptide-presenting B cells with activated Th bearing appropriate TCRs leads to binding of CD40 to CD40 ligand, which induces subsequent activation of transcription factors, B cell proliferation, somatic mutation and production of drug-specific antibodies [6].

Effector phase to high-molecular protein drugs

The event of sensitization is often clinically unapparent. If later exposure to the same allergen occurs, the response is dependent on the type of sensitization. Allergic reactions to protein drugs are mostly antibody mediated. Best

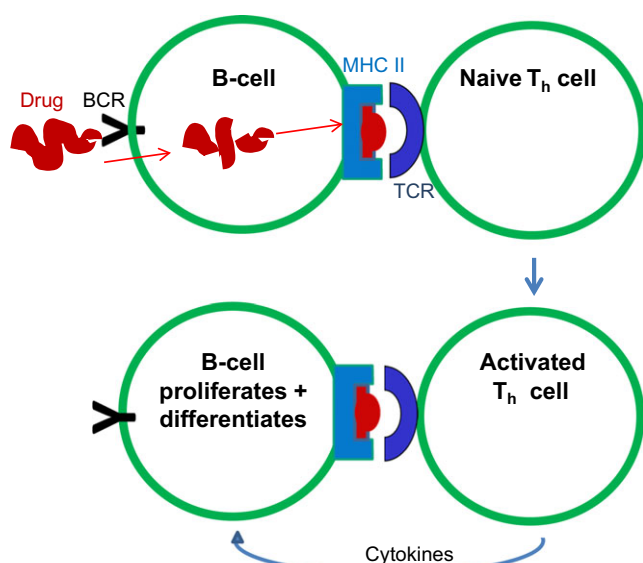


Fig. 1. Mechanism of drug sensitization to high-molecular (protein) drugs. The drug is recognized and endocytosed by a B cell with matching B cell receptor (BCR). This activates the B cell, which processes and presents the antigenic peptide of the drug on its class II major histocompatibility complex (MHC). A naïve T helper(T_h) cell with matching T cell receptor (TCR) gets activated by the MHC-presented antigenic peptide and secretes cytokines that further stimulate B cells into proliferation and differentiation.

studied are IgE-mediated reactions (type I according to the classification of Coombs and Gell [7]), but IgG-mediated immune complex reactions (type III) have also been reported (Table 2).

1 Type I (IgE-mediated allergy): Drug-specific IgE circulates in the blood and binds to IgE-specific receptors (FcεRI) predominately expressed on the surface of mast cells and basophils. During re-exposure, the drug binds to the Fab part of the IgE molecules. The current paradigm postulates that the antigen must be presented in multivalent form to induce an allergic reaction: binding of two or more cell surface-bound IgE molecules (cross-linking) leads to activation of mast cells and release of mediators such as histamine, leukotrienes, prostaglandins and cytokines. This causes vasodilatation, increased vascular permeability, enhanced mucus production, bronchoconstriction

leading to the clinical manifestations of urticaria or anaphylaxis.

2 Type III (IgG immune complex reaction): Formation of immune complexes between drugs and specific antibodies to drugs is common and not necessarily pathogenic. However, immune complexes have also been reported to activate endothelial cells and to induce FcγR-dependent complement activation and deposition in small vessels. Why and under which circumstances immune complex disease develops remains unclear. Clinical symptoms of a type III reaction comprise serum sickness, drug-induced lupus erythematosus and/or vasculitis.

Allergy to low-molecular drugs

Most drugs are low-molecular compounds (mostly < 800D). They are too small to be directly processed and presented by APCs. Sensitization to low-molecular substances has been explained by the hapten and pro-hapten model (Fig. 2) [8].

Sensitization to low-molecular drugs

Haptens are low-molecular substances that can covalently bind to carriers such as proteins or polypeptides. Thereby, they become full allergens, which are able to induce sensitization. After entering in the body, hapten drugs, such as penicillins, can bind covalently to different soluble autologous proteins, for example human serum albumin. These resulting drug–protein compounds (hapten–carrier compounds) can be taken up by APCs, processed and presented on MHC molecules as hapten modified and thus immunogenic peptides. If the drug–carrier compound is a soluble (solved) protein and specifically recognized and presented by B cells, it can induce formation of drug-specific antibodies and immediate-type allergy in the same way as described above for high-molecular protein drugs.

However, haptens can also bind to non-soluble protein structures such as membrane proteins. They might directly modify MHC-associated self-peptides or form carrier–hapten compounds, which are endocytosed and processed by other APCs than B cells [8] such as macro-

Table 2. Overview on effector mechanisms of immunologic drug hypersensitivity reactions (adapted from [6, 15])

Drug size	Mechanism	Submechanism
High molecular	Type I: IgE mediated	Mast cell/basophil release
	Type III: IgG immune complex	Complement activation
Low molecular	Type I: IgE mediated	Mast cell/basophil release
	Type II: IgG-mediated cytotoxicity	Cell lysis
	Type III: IgG immune complex	Complement activation
	Type IV a, b, c, d: T cell mediated	Hapten–carrier dependent Direct pharmacological interaction of drug with immune receptors

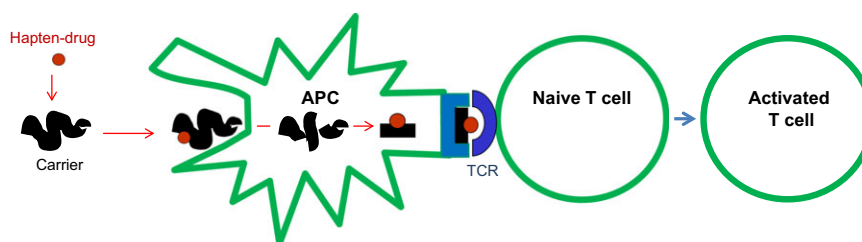


Fig. 2. Mechanism of drug sensitization to low-molecular (hapten) drugs. The drug binds covalently to an autologous carrier protein, which is endocytosed and processed by an antigen-presenting cell (APC). The APC presents the drug-modified peptide on its major histocompatibility complex (MHC) to a T cell with matching specific T cell receptor (TCR). The T cell becomes activated and proliferates. It differentiates depending on the kind of APC and cytokine environment.

phages, dendritic cells or cutaneous Langerhans cells. Depending on the APC and the cytokine environment, hapten-carrier compounds can be recognized by B and T cells with appropriate specificity and induce antibody production (type I-III) or T cell activation (type IV) with differentiation and clonal expansion of different T cell types. Primed T cells can be divided into effector (Teff, which are short living) and effector memory and central memory subsets (TEM and TCM, which are long-living) [9]. These T cell subsets have distinct homing locations. Naïve T cells and TCM home to lymph nodes. Effector T cells (Teff and TEM) interact with tissue-specific ligands, and it is assumed that effector T cells (Teff and TEM) home to where the hapten-carrier compounds derive from [10]. It is thought that most effector memory T cells are resident in the skin [11].

Some drugs, such as sulfamethoxazole, are prohaptenes, drug molecules that are chemically non-reactive in their native form. Sensitization to such inert drugs (prohaptenes) only occurs after metabolism (bioactivation), which transforms them into reactive metabolites (haptens, e.g. nitroso-sulfamethoxazole) [12].

Effector phase to low-molecular drugs

On re-exposure, allergic reactions to low-molecular drugs are dependent on the sensitization pattern and have been divided into four categories (type I-IV) according to Coombs and Gell (Table 2). The vast majority of DAs against low-molecular drugs are presumed to be either IgE- (type I) or T lymphocyte mediated (type IV) [13].

- 1 For type I (IgE-mediated) and type III (immune complex-mediated) reactions, the effector phase is the same as described above for high-molecular drugs.
- 2 Type II (IgG-mediated cytotoxicity) reactions arise, if specific antibodies bind to cell membrane-bound haptens. Different pathways of antibody recognition of target cells have been proposed [14, 15]. Predominant target cells are erythrocytes, leucocytes, platelets and probably hematopoietic precursor cells in the bone marrow. Such antibody-coated cells are sequestered to the reticuloendothelial system in liver and spleen by Fc or complement receptor binding leading to cytopenias

(e.g. thrombocytopenia). More rarely, intravascular destruction by complement-mediated lysis also occurs.

3 T cell-mediated DA (type IV):

i Hapten-carrier-dependent effector mechanism: On renewed exposure, hapten-carrier compounds (specifically drug-carrier compounds) may be presented again on the MHC of different APC and be recognized by specific TCM in draining lymph nodes or by effector T cells (Teff and TEM) in the tissue. Restimulation of TCM in the draining lymph nodes might become clinically manifest as an enlargement of local lymph nodes. Restimulation of effector T cells (Teff and TEM) by hapten-carrier compounds presented on APC will result in local T cell-mediated inflammation in those tissues where the prohapten/hapten-carrier compounds originally were formed and presented during the primary sensitization. Such events are well documented for contact dermatitis and are also seen in some severe systemic DHRs. However, the hapten/prohapten concept is barely adequate to explain the predominance of skin involvement in allergic reactions to systemically administered drug, which are expected to be localized at the site of administration (hapten drugs) or metabolism (prohapten drugs).

ii Direct pharmacological interaction of drug with immune receptors: More recently, a supplementary effector mechanism for non-immediate DA to low-molecular peptide drugs has been described [16], namely the direct pharmacological interaction of native low-molecular drugs with immune receptors (p-i-concept). It can more stringently explain the predominance of skin involvement in allergic reactions to systemically administered drug. The concept is described below in this article under recent insights into mechanisms of immunologic DHRs.

Subclassification of T cell-mediated drug hypersensitivity reactions

Regardless of the hapten- or p-i-dependent mechanism of the effector phase, T cell-mediated hypersensitivity

can be subdivided according to the predominant cell type recruited and activated, which corresponds to typical clinical manifestations. On re-exposure, the resulting clinical reaction is primarily determined by the types of T cells that are sensitized on the types of cells which are presenting the drug epitope and by the cytokine environment. These determine the cytokine pattern which preferentially recruits and activates specific cells [16]:

- 1 Type IVa: Predominance of cytokines and chemokines, which preferentially activate and recruit monocytes, such as typically seen in tuberculin-like reactions
- 2 Type IVb: Predominance of cytokines and chemokines, which preferentially activate and recruit eosinophils, such as seen in typical maculopapular exanthems
- 3 Type IVc: Predominance of cytotoxic functions by either CD4+ or CD8+ T cells, such as seen in bullous exanthems
- 4 Type IVd: Predominance of cytokines and chemokines, which preferentially activate and recruit neutrophils, such as seen in acute generalized exanthematic pustulosis.

Recent insights into mechanisms of immunologic drug hypersensitivity reactions

Cross-reactivity

There are findings which demonstrate that previous contact with a drug may not always be a basic requirement for immunologic DHRs: in 68% of patients with cetuximab-induced anaphylaxis, IgE antibodies specific for galactose- α -1,3-galactose were found [17]. The aetiology may be tick bites [18]. Many patients with allergy to neuromuscular agents were exposed to pholcodine and developed consecutively cross-reactive IgE antibodies [19]. In a study on hypersensitivity to contrast medium, half of the patients reacted on primary exposure [20]. These data suggest that drug-independent cross-reactive antigens may also induce sensitizations, which can manifest as immunologic DHRs.

T cell-mediated drug hypersensitivity by direct pharmacological interaction (p-i-concept)

Investigations of drug-specific human T cell clones (TCC) from drug-allergic subjects revealed reactivity to the causative drug in its native form without the need of being processed or bound stably to a carrier molecule. In cell culture experiments, full reactivity of the TCC was observed within minutes in the presence of both the parent inert drug and the APC with an appropriate MHC where the parent drug could be easily washed away [21, 22]. These findings led to the concept

of a direct pharmacological interaction of drugs with immune receptors (p-i-concept). It postulates that low-molecular drugs attach reversibly to immune receptors such as TCR on T cells or MHC on APCs [16, 23]. This interaction modifies the very low affinity between autologous MHC-peptide compounds and matching TCRs. As a consequence, T cells with appropriate specificity can be stimulated by autologous APCs in the presence of a native low-molecular drug (Fig. 3). T cells may have acquired the appropriate specificity either after priming by cognate hapten-carrier compounds or after priming by accidentally structurally related cross-reactive antigens such as virus antigens. Such cross-reactivities may explain T cell-mediated hypersensitivity reactions on first exposure as have been described for contrast media hypersensitivity reactions [20].

TEM have a lower threshold for reactivation than naïve T cells [24, 25]. Thus, direct pharmacological interactions of native drugs with immune receptors may activate predominately memory T cells. As the skin contains a special large pool of TEM [11] in close apposition to MHC-expressing dendritic cells, stimulation by direct pharmacological interaction can explain the high frequency and predominance of skin involvement in T cell-mediated hypersensitivity reactions.

Recently, a special type of a p-i-dependent mechanism has been described (Fig. 4). The antiviral drug abacavir can non-covalently and specifically attach to the peptide-binding groove of the involved MHC. This binding can modify quantitatively and qualitatively the selection and presentation of peptide ligands necessary for TCR activation [26–28]. In this way, a different

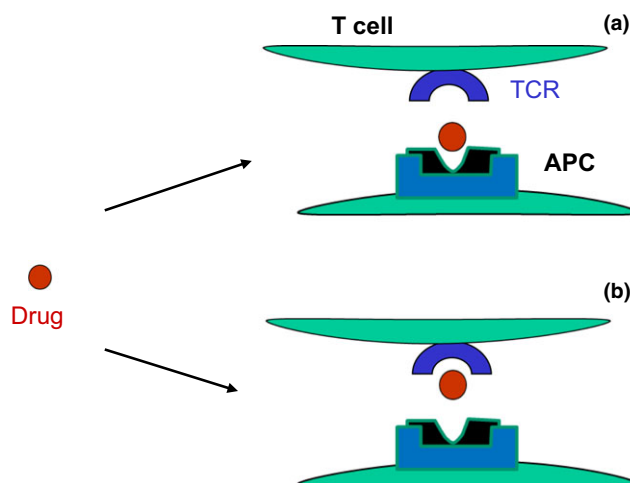


Fig. 3. Direct pharmacological interaction of drugs with immune receptors. A native drug can reversibly attach to the major histocompatibility complex (MHC)-peptide compound (a) or to the T cell receptor (TCR) (b). This alteration enhances the naturally very low affinity between autologous MHC-peptides compounds and a matching TCR so that a T memory with appropriate specificity can be stimulated. In this figure, only the relevant surface portions of the cells are shown.

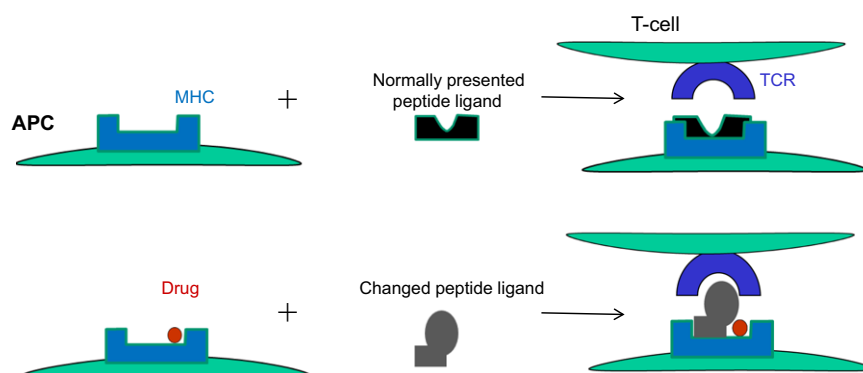


Fig. 4. Drug-induced change of the specific peptide repertoire necessary to activate T cells. A drug can non-covalently attach to the peptide-binding groove of a major histocompatibility complex. This alteration can change the repertoire of the presented matching peptide ligands and may result in auto-reactivity. In this figure, only the relevant surface portions of the cells are shown.

repertoire of self-peptides may be presented to T cells, which may lead to auto-reactivity.

Hepatic tolerance

Clinical and experimental findings point to a pivotal role of the liver for the induction and maintenance of peripheral T cell tolerance. Allogeneic liver transplantation requires less immune-suppression than other transplantations of solid organs and may even induce donor-specific hypo-reactivity [29]. Animal experiments have demonstrated that intrahepatic presentation of an immunogenic peptide or hapten–protein adduct may induce specific T cell tolerance [30, 31]. These findings suggest that intrahepatic presentation of an antigen may induce specific T cell tolerance. Most oral administered low-molecular drugs are predominantly metabolized in the liver, where drug–carriers might also be formed and presented. Consecutively, drug-specific T cell tolerance might be induced. This could explain why liver involvement in DHRs to low-molecular drugs is relatively rare. This mechanism might suppress not only sensitizations to the drug–carrier compound in the liver but also cognate p-i effector reactions. Such a tolerance mechanism might explain why only about 50% of HLA-B*57:1 carriers develop abacavir hypersensitivity upon exposure [32] although abacavir-specific CD8⁺ T cells are detectable in the circulating blood of nearly all B*57:01+ individuals who have never been exposed to abacavir [33, 34].

Genetic factors

The incidence of hypersensitivity varies according to the ethnicity of the patient. There are case reports with familial clustering of drug hypersensitivity, suggesting a genetic predisposition. Genetic analyses revealed particular HLA alleles as predominant genetic susceptibility factors for drug hypersensitivity. Some associations between T cell hypersensitivity and certain HLA haplo-

types have been identified (Table 3). Other genetic associations found so far are less strong and have to be confirmed.

The strongest association is between abacavir and HLA-B*57:01 [35], which has been described above in this article as a special type of p-i-mechanism. Also the association between HLA-B*15:02 and carbamazepine-induced Stevens–Johnson syndrome in Han Chinese seems to involve a similar mechanism as screening of HLA-B*15:02-eluted peptides did not reveal a particular peptide sequence to which carbamazepine could have bound [36]. Very strong associations between HLA haplotype and drug hypersensitivity have been found only for few drugs and so far seem to be exceptions rather than the rule.

Novel drugs

There are many novel drugs such as cytokines, monoclonal antibodies, adoptive cell transfer or antisense oligonucleotides. Adverse side-effects to such drugs are clinically heterogeneous and can be caused by different pathways. Even immune reactions are often not caused by a specific immune response, but correspond to an imbalance of the immune regulation, which is induced

Table 3. Important HLA allele associations with drug-induced hypersensitivity

Drug	Involved HLA	Clinical manifestation	Reference
Abacavir	HLA-B*57:01	Drug hypersensitivity syndrome	[35]
Carbamazepine	HLA-B*15:02	Stevens–Johnson Syndrome	[40]
	HLA-A*31:01	Toxic epidermal necrolysis	[41]
Allopurinol	HLA-B*58:01	Stevens–Johnson Syndrome	[42, 43]
Flucloxacilline	HLA-B*57:01	Drug-induced liver toxicity	[44]

by the pharmacological activity of the causative drug. Such pharmacologically induced reactions may provide important insight into the principle of immune regulation. They may manifest as excessive immune responses (e.g. cytokine storm induced by anti-CD28 monoclonal antibody TGN1412 [37]), as impaired immune functions (e.g. increased risk of serious especially intracellular infection on anti-TNF therapies) or autoimmunity (e.g. autoimmune disorders induced by immune checkpoint inhibitors [38]). However, allergies according to WAO/EAACI nomenclature may also occur. Even in adoptive T cell therapy with chimeric antigen receptor, anaphylaxis has been described, probably through IgE antibodies specific to the chimeric antigen receptors [39]. Nevertheless, well-documented cases with allergy are scarce and the experience from novel drugs has been too small to date to provide truly new insights into the principles of drug allergy (DA).

Conclusions

Drug allergy is the term for the subgroup of immunologic DHRs which are hypersensitivity reactions mediated either by specific antibodies or specific T lymphocytes. Due to the immunologic memory, DA reactions may increase on re-exposure and are therefore dreaded. However, in contrast to allergy against other

elicitors such as foods or insect venom, the majority of DA in clinical practice still cannot be confirmed by existing *in vivo* or *in vitro* allergological tests.

The classification described by Coombs and Gell about 40 years ago is helpful. However, in its old version, it does not explicitly reflect newer insights. Recent findings show that previous contact with a drug may not be a prerequisite for immunologic DHRs. They suggest that drug-independent cross-reactive antigens may induce sensitizations, which than can later manifest as immunologic DHRs. Direct pharmacological interaction (p-i-concept) is a supplementary effector mechanism for T cell-mediated reactions, which may give an explanation for the predominant skin involvement, as this organ is particularly rich in T memory cells in close apposition to MHC-expressing dendritic cells. A special type of direct drug interaction with the MHC may explain the strong HLA associations of immunologic DHRs which have been found for some drugs. The description of direct pharmacological interactions may suggest that the frontiers between specific and unspecific immune reactions are less strict than has been assumed to date.

Conflict of interest

The authors know of no commercial associations that would pose a conflict of interest.

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