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T Cell–Mediated Hypersensitivity Reactions to Drugs

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Abstract

The immunological mechanisms driving delayed hypersensitivity reactions (HSRs) to drugs mediated by drug-reactive T lymphocytes are exemplified by several key examples and their human leukocyte antigen (HLA) associations: abacavir and *HLA-B*57:01*, carbamazepine and *HLA-B*15:02*, allopurinol and *HLA-B*58:01*, and both amoxicillin-clavulanate and nevirapine with multiple class I and II alleles. For HLA-restricted drug HSRs, specific class I and/or II HLA alleles are necessary but not sufficient for tissue specificity and the clinical syndrome. Several models have been proposed to explain the immunopathogenesis of severe T cell–mediated drug HSRs, and our increased understanding of the risk factors and mechanisms involved in the development of these reactions will further the development of sensitive and specific strategies for preclinical screening that will lead to safer and more cost-effective drug design.

Keywords

altered peptide; human leukocyte antigen; major histocompatibility complex; Stevens-Johnson syndrome; toxic epidermal necrolysis; pharmacogenomics

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INTRODUCTION

Drug hypersensitivity reactions (HSRs) are a type of adverse drug reaction (ADR) associated with high global morbidity and mortality and often lead to drug withdrawal after significant investment in drug development. There is thus an unmet need to understand both patient- and drug-related risk factors and mechanisms involved in these reactions. A better understanding of HSRs will aid in the development of preclinical screening programs to enable safer, faster, and more cost-effective drug design.

Immune-mediated reactions, sometimes referred to as drug allergy, comprise <20% of all ADRs. These reactions have traditionally been labeled idiosyncratic or unpredictable hypersensitivity reactions, and are classified as Type B reactions. The most clinically relevant immune-mediated Type B ADRs are the Type I or Type IV hypersensitivity reactions according to the Gell-Coombs system classification (1). Type I reactions are immediate, IgE-mediated reactions, usually occurring within 1 h after drug administration, and mainly cause urticaria, anaphylaxis, and bronchospasm. Penicillin allergy is an example of a Type I ADR commonly seen in clinical practice. Type IV reactions, in contrast, are delayed hypersensitivity reactions mediated by drug-reactive T lymphocytes (1). Delayed drug reactions can represent an additional diagnostic challenge when multiple drugs are given together, as the last drug is often not the one causing the HSR. Type IV reactions have received heightened interest recently with the discovery that many are associated with class I and/or II human leukocyte antigen (HLA) alleles. This association has led to insights into the immunopathogenesis of HSR syndromes and to HLA-allele-specific screening for the prevention of these serious reactions. Examples of the latter include screening for *HLA-B*57:01* to avoid abacavir hypersensitivity reaction (ABC HSR), which is routine in HIV clinical practice, and for *HLA-B*15:02* to avoid carbamazepine-associated Stevens-Johnson syndrome/toxic epidermal necrolysis (CBZ SJS/TEN) in Asian populations.

DELAYED DRUG HYPERSENSITIVITY REACTIONS

Delayed HSRs include SCAR (severe cutaneous adverse reaction), SJS/TEN, AGEP (acute generalized exanthematous pustulosis), and DRESS/DIHS/HSS (drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome/hypersensitivity syndrome) (2). ABC HSR is another hypersensitivity reaction that does not clinically fit into any of these categories and is characterized by initial fever, malaise, systemic features and mild to moderate rash is a later feature in 70% of cases. In addition, delayed HSRs can manifest as single-organ involvement, most commonly drug-induced liver disease (DILI) with pancreatitis and tubulointerstitial nephritis as other examples (Table 1) (2).

ESTABLISHED MODELS OF DRUG HYPERSENSITIVITY REACTIONS

T cells usually recognize foreign peptides of at least seven amino acids in length. Several models have been proposed to explain how much smaller synthetic compounds are recognized by T cells and how they are able to elicit an immune response. In support of an adaptation of conventional presentation of peptides together with HLA molecules from antigen-presenting cells, there are many well-characterized examples of drug

hypersensitivity with strong HLA associations. These include the associations of *HLA-B*57:01* with ABC HSR, *HLA-B*15:02* with CBZ SJS/TEN, *HLA-B*58:01* with allopurinol-associated SJS/TEN and DRESS/DIHS, and most recently *HLA-B*13:01* with dapsone-associated DRESS/DIHS (Table 2, Figure 1). Although there are many other examples of delayed drug HSRs that exhibit both class I and II HLA associations, examining these very strong drug–HLA associations sheds light on the general mechanisms that are important in the development of drug hypersensitivity (Figure 1) (3–20).

The main models initially proposed to explain how drugs interact with the immune system included the hapten/prohapten hypothesis and the “pharmacological interaction of drugs with immune receptors” (P-I) model (Figure 2*a*). Haptens are chemically reactive small molecules that can form stable covalent bonds with larger proteins or peptides. Haptenation results in alteration of autologous proteins, which may lead to the generation of drug-specific humoral or cellular immune responses. A well-characterized example of haptenation is covalent binding of penicillin derivatives to lysine residues of serum albumin resulting in antibody recognition (21). In addition, many drugs are not chemically reactive but induce immune-mediated side effects after their metabolism. An example of such prohapten modification is the metabolism of sulfamethoxazole by CYP2C9 in the liver to produce sulfamethoxazole-nitroso by oxidation, which then binds to intracellular proteins (22). In contrast to the hapten model, the P-I concept holds that a drug in its native form can bind directly to immune receptors such as the T cell receptor (TCR) or to certain HLA molecules via noncovalent bonds without the need for a peptide (23). In the case of a drug HSR, the binding of the drug to immune proteins must be sufficient to transmit a stimulatory signal via the TCR.

EXTENDING MODELS OF DRUG–HLA–PEPTIDE INTERACTION

The Altered Peptide Repertoire Model

Abacavir (ABC) is a guanosine analogue associated with a hypersensitivity syndrome characterized predominantly by fever, malaise, gastrointestinal symptoms in up to 8% of those starting treatment, and a late mild–moderate rash in ~70% of patients (24). A strong association between the HLA class I allele *HLA-B*57:01* and ABC HSR was reported in 2002 (7, 8). Since then, clinical studies confirmed that 100% of patch test–positive patients with a clinical history of ABC HSR carried *HLA-B*57:01* (25–29). The high specificity of ABC patch testing for ABC HSR together with the 100% negative predictive value (NPV) and the high positive predictive value (PPV) of 55% of *HLA-B*57:01* for ABC HSR made this an excellent model to study mechanisms underlying HLA-linked HSRs (Table 2). Laboratory evidence has shown that ABC HSR is *HLA-B*57:01* restricted and mediated by CD8⁺ T lymphocytes (30). In addition, CD8⁺ T cells from ABC-naïve patients carrying the *HLA-B*57:01* allele proliferate in response to ABC in long-term culture and are specifically activated by the drug. These T cells display a polyclonal response with the broad use of V beta T cell receptors (30). Modeling and crystallography data have provided evidence that ABC binds noncovalently to the floor of the peptide-binding groove of *HLA-B*57:01*, altering the chemistry and shape of the antigen-binding cleft (31–33). This ABC binding alters the repertoire of self-peptides presented by *HLA-B*57:01* such that peptides with a

small aliphatic residue at the C terminus (e.g., valine, alanine, or isoleucine) are favored in comparison to peptides with tryptophan or a phenylalanine, which are normally bound to unmodified *HLA-B*57:01* molecules (31–33); 25–45% of the new self-peptides are presented only in the presence of ABC. Such peptides will not have been presented during thymic development of T cells when self-reactive T cells are negatively selected, and thus at least some of these self-peptides have not been previously tolerized and may be recognized by T cells of hypersensitive patients (31–33). This provides a new model for HLA-associated drug HSRs termed the altered peptide repertoire model (Figures 2a and 3).

Limitations of Drug–HLA Interactions Models

We have seen that the interaction of a drug with a specific HLA allele can be explained either by a haptenated peptide or noncovalent binding of drug to the HLA or TCR, with or without the involvement of an endogenous peptide. However, these fail to explain why not all patients with the HLA allele exposed to the drug develop hypersensitivity, nor why different drug–HLA allele combinations result in such different clinical syndromes (Table 2).

The Heterologous-Immunity Model as an Extension of HLA–Drug-Binding Models

The immune system has evolved to eliminate foreign pathogens with many safeguards to prevent damage to self. To initiate the afferent arm of the T cell response, several signals need to be triggered in the correct order and place to generate cytotoxic T cells at the site where they are needed. The simple presence of a small-molecular drug capable of interacting with HLA or an HLA-presented peptide is less likely to drive the production and trafficking of potentially tissue damaging T cells than are peptides containing an authentic pathogen that is infecting and killing cells. The term heterologous immunity in general refers to the situation where such T cells elicited by one epitope (e.g., from a pathogen) cross-recognize a different epitope (e.g., from another pathogen or from a neo-antigen). Organ transplantation, like drug hypersensitivity, represents a unique circumstance where a plethora of neo-antigens to which the host has not been tolerized are presented to the immune system. In that setting, it has been demonstrated that pre-existing class I-restricted effector memory T cell responses to prevalent viral infections, most commonly to one of the human herpesviruses (HHV), mediate organ rejection (34–41). Similarly, in the drug hypersensitivity setting, memory T cells that are specific for, e.g., HHV peptides may cross-react with endogenous peptides presented in the presence of a drug through any of the mechanisms depicted in Figure 2a, e.g., novel peptides that are presented in an altered-repertoire fashion, drug haptenated proteins, or directly activated by drug binding in a P-I manner (Figure 2b). Thus, the presence or absence of a preexisting heterologous immune response could determine whether an individual with a risk-conferring HLA allele develops a severe drug HSR.

Recent studies of tissue-resident memory T cells have provided additional insights into how HHV can drive the production of T cells with a high cytolytic potential and low threshold to be triggered to cause local tissue damage. For example, herpes simplex virus (HSV)–specific CD8 $\alpha\alpha^+$ tissue-resident T cells persist in the epidermis for prolonged time periods and cause rapid cytotoxicity to cells expressing low levels of HSV reactivation (42).

THE SIGNIFICANCE OF THE T-CELL RECEPTOR

Carbamazepine-associated Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis

CBZ is an aromatic amine anticonvulsant and mood-stabilizing drug associated with SJS/TEN, and this example has provided further insights into potential mechanisms driving drug HSRs, particularly the central role of the specificity of the TCR in such reactions. CBZ SJS/TEN is associated with the carriage of *HLA-B*15:02* and other HLA-B alleles of the B75 serotype, such as *HLA-B*15:21*, *HLA-B*15:11*, and *HLA-B*15:08* (43, 44). This association has been extended to include other antiepileptic drugs with similar structures, such as phenytoin, lamotrigine, and oxcarbazepine (45). Although the PPV for *HLA-B*15:02* and CBZ SJS/TEN is much lower than that for *HLA-B*57:01* and ABC HSR (Table 2), screening strategies for the alleles have been initiated in Chinese and other Asian populations where the B75 alleles are most prevalent (46). *HLA-A*31:01* has also been associated with CBZ SJS/TEN in Europeans and Japanese in some but not all studies (11, 47, 48). Others have reported an association of *HLA-A*31:01* with CBZ DRESS but not SJS/TEN (49, 50). Recent evidence suggests that this HLA-A association may in fact be due to linkage disequilibrium of *HLA-A*31:01* with *HLA-DRB1*04:04* (51, 52). This possibility needs to be explored further with careful haplotype mapping or experimental studies.

The TCR repertoire has been the focus of mechanistic research in CBZ SJS/TEN. CBZ-specific CD8⁺ T cells have been isolated from patients with SJS, and in vitro exposure of these cells to CBZ was shown to activate the release of granulysin (53). A dominant TCR, Vβ-11 clonotype Vβ-11-ISGSY, was identified in blister fluid and peripheral blood mononuclear cells (PBMCs) in 84% of patients with SJS/TEN and in 14% of healthy controls, and was absent in controls with CBZ tolerance. Furthermore, CBZ-dependent cytotoxicity can be blocked by anti-TCR-Vβ-11 antibodies in these cells. Finally, both a VB-11-ISGSY clone and specific Vβ-11-ISGSY transfectants display cytotoxicity against *HLA-B*15:02* antigen-presenting cells in the presence of CBZ (53). The significance of other TCR clonotypes from the blister fluid of CBZ SJS/TEN patients is currently under study.

The structural basis of the CBZ-HLA interactions is not defined as it is for ABC-HLA interactions (31, 32). Although CBZ alters the repertoire of peptides eluted from *HLA-B*15:02* (31), lysis of CBZ-loaded target cells by the CBZ-reactive CD8⁺ T cell lines does not seem to require the presence of peptide. It is therefore possible that CBZ could directly interact with the TCR in an *HLA-B*15:02*-restricted fashion, in comparison to the ABC-peptide-*HLA-B*57:01* model. A specific population of cytotoxic lymphocytes that exhibit cytotoxicity against B lymphoblastoid cell lines or keratinocyte transfectants that express the *HLA-B*15:02* allele can be blocked by anti-HLA-B antibodies (54). Site-directed mutagenesis has shown that the residues (Asn63, Ile95, and Leu156) in the peptide-binding groove of *HLA-B*15:02* are involved in CBZ presentation and cytotoxic T lymphocyte activation. Asn63 of the B pocket shared by members of the B75 family is the key residue (54). It has also been independently predicted that CBZ binds beneath the P4/P6 residues of the peptide, adjacent to position 156 (31).

PHENOTYPE SPECIFICITY, HLA CLASS I AND II HAPLOTYPES, AND METABOLISM

Nevirapine

Nevirapine (NVP) is a non-nucleoside reverse transcriptase inhibitor known to cause DRESS, SJS/TEN, and DILI. NVP HSR differs from other well-characterized HLA-associated HSRs as it shows subphenotype-specific associations across both class I and Class II HLA alleles. The first identified association with NVP HSR was the hepatotoxicity subphenotype with *HLA-DRB1*01:01* and CD4% 25 (15). Since the first report multiple HLA associations have been identified and these appear to be dependent upon both ethnic group and subphenotype. The most frequently reported however are *HLA-C*08* with NVP HSR in Europeans, *HLA-B*35:05/35:01* with cutaneous NVP HSRs in Asian and Caucasian populations, respectively, and *HLA-C*04* also with cutaneous NVP HSRs across several ethnic groups (16, 55–62).

The complexity of the haplotype and phenotype associations for NVP HSR may be due to pre-existing pathogen-induced tissue-specific T cell responses that can be restimulated by the drug. In keeping with this, both CD4⁺ and CD8⁺ T cells from NVP HSR patients' PBMCs produce INF γ in response to NVP stimulation. Cell depletion studies have shown that an optimal response is dependent on the presence of both CD8 and CD4 T cells and that INF γ release due to NVP stimulation of PBMCs can be completely abrogated by either CD4 or CD8 depletion in some patients (62). Furthermore, in support of an immune response to drug-related neo-antigen, the CD4⁺ T cell population contains central memory cells that produce IL-2 after NVP stimulation. Of clinical significance is a recent case of NVP HSR in a five-month-old infant who carried *HLA-C*04*; CD8⁺- and CD4⁺-specific responses to NVP were demonstrated, with clinical features of fever, rash, eosinophilia, and hepatitis similar to those in a more mature immune system (62). There is a move toward treatment of infants with NVP-based antiretroviral therapy as early as possible following delivery, and typically within hours of birth, based on reports of potential HIV clearance/eradication after initiation of NVP therapy at birth in at least two cases (63, 64). HLA characterization may be helpful in this regard.

Adding another level of variability in drug HSRs, drug metabolism has been shown to be independently related to NVP HSR. Slow-metabolizer phenotypes for *CYP2B6* have been associated with NVP HSR with rash in African populations (65). The *CYP2B6 516G→T* together with the carriage of *HLA-C*04* in Blacks or *HLA-B*35* and *HLA-C*04* in Asians shows a stronger association with cutaneous phenotypes of NVP HSR than when the alleles are considered alone (16). Slow metabolizers of *CYP2B6* have a slower clearance rate for the parent drug (66, 67). A high level of parent drug is likely to facilitate noncovalent binding to HLA, peptide, or TCR. Cell studies have shown that INF γ is produced in NVP HSR patients' PBMCs in the presence of NVP but not 12-OH-NVP (62).

Amoxicillin-Clavulanate

Like NVP, amoxicillin-clavulanate (AC) shows phenotype-specific HLA associations with DILI across both class I and class II HLA alleles. The AC DILI phenotype may vary in the

time to onset and the pattern of injury, presenting as either hepatocellular or cholestatic/mixed liver damage. Initial studies reported the *DRB1*15:01-DRB5*01:01-DQB1*06:02* haplotype associated with AC DILI (12–14), and this was confirmed by a genome-wide association study (GWAS) that also showed a significant association with class I *HLA-A*02:01* as an extension of this haplotype (68). Recently, a study focusing specifically on phenotypic features of AC DILI and their HLA associations confirmed the *DRB1*15:01-DRB5*01:01-DQB1*06:02* haplotype as significant and found that it associated in particular with the cholestatic/mixed type of injury and a tendency for a longer delay of onset (69). The same study also reported a predominance of the hepatocellular type of injury in *HLA-A*30:02* and/or *-B*18:01* carriers, reflected in significantly higher alanine aminotransferase levels. These alleles were also significantly associated with delayed onset (69). The specific class I and II HLA allele associations with the hepatocellular or cholestatic/mixed liver damage phenotypes may suggest tissue-specific T cell responses are significant in AC DILI. Further supporting a TCR-based mechanism for AC DILI, the GWAS also found a positive association with the single-nucleotide polymorphism (SNP) *rs2476601* within the *PTPN22* gene (odds ratio = 2.1, C > T SNP), which acts as a negative regulator of TCR signaling by direct dephosphorylation of key TCR complex signaling molecules (68).

DIRECT T CELL RECEPTOR ACTIVATION?

Allopurinol (ALP) is a xanthine oxidase inhibitor with an HSR characterized by fever, rash, and hepatitis that can be accompanied by other organ involvement such as interstitial nephritis. ALP HSR occurs in ~2% of those starting the drug (Table 1). Less commonly, ALP has been associated with SJS/TEN. A strong association has been reported between *HLA-B*58:01* and both the DRESS/DIHS and SJS/TEN associated with ALP. There has been increased impetus for screening for *HLA-B*58:01*—particularly in populations where *HLA-B*58:01* is prevalent, such as those of Han Chinese and Thai ancestry—as it is strongly associated with both SJS/TEN and DRESS in these populations (3, 70, 71) (Table 2). Cost-effectiveness studies are ongoing. Since the advent of *HLA-B*15:02* screening in Taiwan, ALP has become the most common cause of SJS/TEN. The *HLA-B*58:01* allele has high NPV for SCAR in these populations and a PPV of ~3% (Table 2). Among non-Asian patients with ALP HSRs, many do not have *HLA-B*58:01*, so other significant allele or haplotype associations may yet be identified. Similar to NVP, the metabolism and dose of ALP is significant in the development of the HSR as the metabolite oxypurinol (OXP) drives the T cell response to the drug (72, 73). ALP is rapidly metabolized to OXP via aldehyde oxidoreductase and xanthine oxidoreductase within 2 h of oral administration, whereas OXP is slowly excreted by the kidneys over 18–30 h (74).

Cellular studies support OXP as the component responsible for ALP HSR. Lymphocytes from HSR patients are moderately stimulated by ALP and markedly stimulated by OXP, showing enhanced expression of activation markers and proliferation in the presence of the metabolite (73, 75). Both drugs induce cytotoxicity, but cross-reactivity is not seen between ALP-specific T cell lines and OXP-specific T cell lines (73). In a recent study, OXP-specific T cell lines could be activated in the absence of antigen-presenting cells, suggesting that a direct P-I interaction might occur between OXP and the TCR. The authors suggest that peptides may undergo partial displacement in the presence of OXP and the peptide-binding

groove may undergo conformational changes to accommodate the drug-peptide (76). If the model is correct, these altered conformations of the presented autologous peptides, together with drug–HLA complexes, may trigger an immune response (77), in a similar manner to the altered peptide repertoire model. The same study also examined T cell responses elicited by ALP or OXP, and these were not limited to particular TCR V β repertoires.

All OXP-specific T cell lines from *HLA-B*58:01* donors were restricted exclusively to *HLA-B*58:01* for the drug recognition. Molecular docking and modeling supported OXP–*HLA-B*58:01* interactions within the F pocket of the peptide-binding groove of *HLA-B*58:01*. OXP may form van der Waals interactions with the surrounding residues of the F pocket and a hydrogen bond with Arg97. Supporting the specificity of this interaction, in *HLA-B*57:01*, Arg97 is replaced by Val97, weakening OXP binding (77).

CONCLUSIONS AND FUTURE DIRECTIONS

Man-made small molecules and/or their metabolites can interact with HLAs to cause dangerous T cell–mediated hypersensitivity syndromes. In particular, we have described the interactions of ABC, CBZ, and OXP with *HLA-B*57:01*, *HLA-B*15:02*, and *HLA-B*58:01*, which cause T cell–mediated HSRs in 55%, 3%, and 3% of exposed individuals, respectively. Specific combinations of class I and/or II MHC alleles are associated with specific subphenotypes of NVP hypersensitivity. In each case, the drug and the specific class I or II HLA allele(s) are necessary but not sufficient to explain the tissue specificity and clinical syndrome. Some other factor must be present. In CBZ-induced SJS/TEN, one such factor may be that pre-existing tissue-resident memory T cells with a specific TCR can cross-recognize CBZ presented by keratinocytes in the context of *HLA-B*15:02*. The alternative to this heterologous immune model is that the drug induces T cells with this TCR of its accord from the naïve T cell pool.

The hapten model accounts for IgE-mediated reactions, where a drug like penicillin covalently binds with a protein to form a stable conformational B cell epitope. Noncovalent binding of a drug to HLA-allele(s) may result in severe T cell–mediated hypersensitivity if cytotoxic T cells are triggered by TCR activation. It remains contentious whether classical antigen presentation or peptide is required for such T cell activation, but it is clear that high extracellular levels of the relevant drug or metabolite favor noncovalent binding and T cell activation (79, 80).

Understanding the specific mechanisms by which drugs interact with the immune system to cause allergic disease will be important in predicting which drugs are likely to cause these syndromes and the specific human immunogenetic risk factors involved. Currently, it appears that HLA alleles are necessary but not sufficient for these severe T cell–mediated drug reactions and that class I HLA-associated drug HSRs are the most severe (Figure 1). Although large studies have demonstrated the clinical utility of screening for *HLA-B*57:01* to prevent ABC HSR, this strategy will probably not be viable for most other drugs. Ideally, the HLA risk factors and the drugs likely to cause HSRs should be identified preclinically, before significant investment in drug development and well before any human morbidity or mortality can result. Identification of the highest risk drug and HLA risk factors (e.g., HLA-

B alleles strongly associated with various subphenotypes of hypersensitivity) could lead to a viable first-line screening strategy to identify the highest-risk drugs prior to human use with a more extensive second-line strategy to be deployed at the first signal of a severe immunologically mediated drug reaction in premarketing studies or postmarketing surveillance. In addition, the role of the TCR is important, and an increased understanding of the heterologous immune model of drug hypersensitivity will aid in our understanding of the basis of cross-reactive memory T cell responses and why some but not all patients with a specific HLA allele will develop a drug HSR.

Glossary

ABC	abacavir
CBZ	carbamazepine
SJS/TEN	Stevens-Johnson syndrome/toxic epidermal necrolysis
SCAR	severe cutaneous adverse reaction
DRESS	drug reaction with eosinophilia and systemic symptoms
DIHS	drug-induced hypersensitivity syndrome
DILI	drug-induced liver disease
TCR	T cell receptor
NPV	negative predictive value
PPV	positive predictive value
NVP	nevirapine

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HLA and severe T cell–mediated drug hypersensitivity

Figure 1.

Timeline of class I and II HLA associations with key examples of drug hypersensitivity reactions (HSRs). The discovery of the association of abacavir hypersensitivity and *HLA-B*57:01* was the breakthrough observation that first linked drug hypersensitivity to class I–restricted, T cell–driven mechanisms (7, 8). Since then, associations between class I HLA alleles and severe immunologically mediated drugs reactions have dominated. The early examples of carbamazepine and *HLA-B*15:02* in SJS/TEN (Stevens-Johnson syndrome/toxic epidermal necrolysis) in Asians and allopurinol and *HLA-B*58:01* and SCAR (severe cutaneous adverse reactions) have also provided key insights into HSR pathogenesis (3, 4,

9–11). In some examples, such as amoxicillin-clavulanate drug-induced liver disease in Northern Europeans, class I/II pairings appear important, whereas others, such as nevirapine hypersensitivity with hepatotoxicity phenotype, appear restricted primarily to class II HLA (5, 6, 11–18, 31, 32).

Figure 2.

(a) Established models of T cell-mediated drug hypersensitivity. (i) In the hapten/prohapten model, drugs form covalent bonds with endogenous proteins/peptides. The drug-modified peptides are then processed by antigen-presenting cells (APC) and presented on the major histocompatibility complex (MHC), resulting in a T cell response. (ii) In the P-I model, the drug in its native form is able to bind directly to immune receptors such as the T cell receptor (TCR) via noncovalent bonds without a peptide. Dashed lines represent noncovalent bonds. (iii) In the altered peptide repertoire model, the drug forms noncovalent bonds within the binding pocket(s) of the MHC to alter the chemistry of the binding cleft and repertoire of self-peptides that can bind to the HLA molecule in question. Some of these newly presented self-peptides have not been previously tolerized, and their presentation results in a T cell response. Adapted from Reference 78 with permission. (b) The heterologous immunity model of drug hypersensitivity. In this model, tissue-specific memory T cells reside at specific sites following a viral infection. These memory T cell subsets may cross-react with (i) drugs binding noncovalently to the TCR and/or the MHC in a P-I manner to activate the T cell directly without the involvement of peptide, (ii) endogenous peptides presented in an "altered peptide repertoire" fashion, (iii) a change to the conformation of the binding pocket with partial peptide binding with or without a direct effect from the drug, or (iv) haptenated endogenous peptides that bind to the TCR. Dashed lines represent noncovalent bonds.

Figure 3.

(a) Crystal structure of the abacavir-peptide-MHC complex reveals intermolecular contacts within the antigen-binding cleft of HLA-B*57:01. Diagram of HLA-B*57:01 in gray. The synthetic peptide HSITYLLPV is shown in cyan carbons. Abacavir is shown as orange for carbon, blue for nitrogen, and red for oxygen. The residues that distinguish the abacavir-sensitive allele *HLA-B*57:01* from abacavir-insensitive *HLA-B*57:03* are shown in magenta for carbon, blue for nitrogen, and red for oxygen. Abacavir forms hydrogen-bond interactions (black dashes) with both the peptide and HLAB*57:01 (32). (b) Model of abacavir-peptide-MHC complex interacting with the T cell receptor. HLA-B*57:01 is depicted in gray. The peptide HSITYLLPV is shown in cyan carbons. Abacavir is shown as spheres: orange for carbon, blue for nitrogen. The T cell receptor is shown in pink.

Table 1
Key features of HLA-associated drug hypersensitivity reactions (2–20, 24–29, 55–58, 61, 67)

Adverse drug reaction	Time to onset	Prognosis	Symptoms/features	Associated drugs	HLA association
SJS/TEN	Within 2 months (shorter for many drugs, e.g., 4 days–2 weeks)	1–5% mortality for SJS, 30–50% for TEN	Skin detachment varying according to body surface area (BSA) involved: 1–10% BSA in SJS, 10–30% BSA overlap, and >30% BSA for TEN. Mucous membrane involvement, fever, liver chemistry elevations, intestinal and pulmonary manifestations and lymphopenia. Fever and mucosal involvement may precede rash.	Allopurinol, aromatic amine anticonvulsants (e.g., carbamazepine, eslicarbazepine acetate, oxcarbazepine, fosphenytoin, phenytoin, phenobarbital, lamotrigine), antiretrovirals (particularly nevirapine), NSAIDs, sulfa antimicrobials	Class I
AGEP	Within 1–3 days of drug initiation for some drugs (e.g., aminopenicillins and other antibiotics); within first to second week for others (e.g., hydroxychloroquine, diltiazem)	Resolution within 15 days after drug removal	Widespread edematous erythema followed by a sterile pustular eruption, fever, and possible eosinophilia	Beta-lactam antibiotics, quinolones, hydroxychloroquine, pristinamycin, sulfa antimicrobials, diltiazem, and terbinafine. Also triggered by infections, nondrug antigens, and viral reactivation	Unknown
DRESS/DIHS/HSS	2 or more weeks after drug initiation	Potentially life threatening	Fever, rash, eosinophilia and/or atypical lymphocytosis, cutaneous involvement and hepatitis. Viral reactivation of HHV6/7, EBV or CMV 2–3 weeks following onset possible. Delayed autoimmune disease	Sulfa antimicrobials, aromatic amine anticonvulsants, beta-lactam antibiotics, vancomycin, allopurinol, NSAIDs, antiretrovirals	Class I/II
DILI	Latency period can be short, intermediate (1–8 weeks), or long (1–12 months). A delayed reaction can occur up to 3–4 weeks after initiation or after drug has been stopped	Potentially life threatening	Acute hepatitis and/or cholestasis	Flucloxacillin, amoxicillin-clavulanate, lumiracoxib, ximelagatran, lapatinib	Class I, class II, or class I/II pairing
ABC HSR	Within 3 weeks of treatment. Patients now screened for HLA-B*57:01	Potentially life threatening with continued treatment. Hypotension, shock described on rechallenge	Fever, malaise, gastrointestinal symptoms, late mild–moderate rash	Abacavir; similar syndromes have rarely been described for azathioprine and trimethoprim-sulfamethoxazole	Class I

Abbreviations: ABC HSR, abacavir hypersensitivity reaction; AGEP, acute generalized exanthematous pustulosis; DIHS, drug-induced hypersensitivity syndrome; DILI, drug-induced liver disease; DRESS, drug reaction with eosinophilia and systemic symptoms; HLA, human leukocyte antigen; HSS, hypersensitivity syndrome; NSAIDs, nonsteroidal anti-inflammatory drugs; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis.

Table 2

Key characteristics of well-defined HLA-associated drug hypersensitivity reactions (3–11, 24–29, 70, 71)

Drug and Syndrome	HLA allele	HLA carriage rate	Disease prevalence	OR	NPV	PPV	NNT to prevent "1"
Abacavir ABC HSR	B*57:01	5–8% Caucasian <1% African 2.5% African American	8% (3% true HSR and 2–7% false positive diagnosis)	960	100% for patch test confirmed	55%	13
Allopurinol SJS/TEN and DRESS/DIHS	B*58:01	9–11% Han Chinese 1–6% Caucasian	1/250–1/1,000	>800	100% in Han Chinese	3%	250
Carbamazepine SJS/TEN	B*15:02	10–15% Han Chinese <0.1% Caucasian	<1–6/1,000 (Han Chinese)	>1000	100% in Han Chinese (with other B75 serotype)	3%	1,000
Dapsone DRESS/DIHS	B*13:01	2–20% Chinese 28% Papuan/Australian Aborigina 0% European/African 1.5% Japanese	1–4% Han Chinese	20	99.8%	7.8%	84
Flucloxacillin DILI	B*57:01	As above	8.5/100,000	81	99.99%	0.12%	13,819

Abbreviations: DIHS, drug-induced hypersensitivity syndrome; DILI, drug-induced liver disease; DRESS, drug reaction with eosinophilia and systemic symptoms; HLA, human leukocyte antigen; HSR, hypersensitivity reaction; HSS, hypersensitivity syndrome; NNT, number needed to treat; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis.