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Review

Human leukocyte antigen and idiosyncratic adverse drug reactions

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ABSTRACT

A clinical association between a specific human leukocyte antigen (HLA) allele and idiosyncratic adverse drug reactions (IADRs) is a strong indication that IADRs are mediated by the adaptive immune system. For example, it is well-established that HLA-B*15:02 and HLA-B*57:01 are associated with carbamazepine-induced Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and abacavir-induced hypersensitivity/flucloxacillin-induced liver injury, respectively. Drug-specific T-cells whose response is restricted by specific HLA risk alleles have been detected from IADR patients, also suggesting an adaptive immune pathogenesis. T-cells from carbamazepine SJS/TEN patients are activated by direct pharmacological interaction between carbamazepine and HLA-B*15:02 expressed on antigen presenting cells (APCs). Abacavir-specific, HLA-B*57:01-restricted T-cells are activated by APCs presenting peptides which are only displayed by the HLA molecule when abacavir is bound during peptide loading. Finally, HLA-B*57:01-restricted activation of T-cells from patients with flucloxacillin-induced liver injury is dependent on processing of drug protein adducts. Based on these observations, it is now possible to utilize blood from healthy drug-naïve volunteers to study the priming of naïve T-cells to drugs. Future development of these methodologies may lead to the development of assays that predict intrinsic immunogenicity of drugs and chemicals at the preclinical stage of drug development.

1. Introduction

Idiosyncratic adverse drug reactions (IADRs) refer to adverse reactions that do not occur in most patients at any dose of the drug, and typically have a delayed onset of weeks to months after initial exposure [1]. IADRs are a major clinical problem in terms of patient morbidity, mortality, cost to healthcare systems, and failure of drugs in development. The skin and liver are most commonly implicated in IADRs and severe cutaneous adverse reactions (SCARs) and drug-induced liver injury (DILI) are most forms. SCARs particularly Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are serious and life-threatening conditions [2] and DILI is the most frequent reason for withdrawal of an approved drug from the market and also a major cause of attrition in drug development [3].

In recent years, retrospective Genome Wide Association Study (GWAS) have identified human leukocyte antigens (HLAs) as an important genetic marker for IADRs, especially for SCARs and for DILI (reviewed in Refs. [4–6]). HLA is necessary for antigen presentation system so the clinical associations provide persuasive evidence to hypothesize that the reactions involve the drug-specific activation of the adaptive immune system. Moreover, mechanistic studies using T-cells from these patients who express risk HLA provide direct evidence to support this [7–9]. Thus, HLA is a promising starting point that must be considered when attempting to develop diagnostic tests that define whether an IADR to a new drug candidate is truly the culprit drug, or to develop pharmacogenetics tests (which might be point of care) for patients to prevent these reactions at clinical stage, or to establish novel *in vitro* model systems to predict IADRs at preclinical stage.

In this review, we summarize recent progress describing clinical HLA associations with IADRs, the latest mechanistic studies using patient samples which link expression of an HLA risk allele to

Abbreviations: APC, antigen presenting cell; BB, Bandrowski's base; DILI, drug-induced liver injury; GWAS, Genome Wide Association Study; HLA, human leukocyte antigen; IADRs, idiosyncratic adverse drug reactions; MHC, major histocompatibility complex; PBMC, peripheral blood mononuclear cell; p-i, pharmacological interaction; PPD, p-phenylenediamine; SCARs, severe cutaneous adverse reactions; SJS, Stevens-Johnson syndrome; SMX-NO, nitroso sulfamethoxazole; TEN, toxic epidermal necrolysis; TCR, T-cell receptor.

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antigen-specific T-cell activation, and discuss the possibility for developing a predictive tool for IADRs using healthy volunteer samples at the preclinical stage.

2. Clinical association between HLAs and IADRs

The HLA system is a gene complex encoding the major histocompatibility complex (MHC) proteins in humans. These cell-surface proteins are responsible for the regulation of the immune system by presenting antigenic peptides to T-cells. The antigen peptide presented by MHC class I (HLA-A, HLA-B, HLA-C) and class II (HLA-DR, HLA-DQ, HLA-DP) are derived from endogenously expressed protein and internalized exogenous protein, and are presented to CD8+ and CD4+ T-cells, respectively. The peptides presented by the HLA are affected by these polymorphisms in multiple ways. Mainly polymorphisms alter the shape and electrochemistry of pockets within the peptide-binding groove that subsequently determine the repertoire of peptides that can bind to a given HLA molecule. Each HLA allotype possesses a specific peptide-binding motif, which can be characterized via sequencing of peptides bound within the cleft [10,11]. Although polymorphism of HLA alleles has been established to drive peptide ligand diversity [12–14], its impact on interactions with small molecule drugs is largely unknown. In the first section of the review we summarize recent clinical associations between HLA molecules and small molecule drug hypersensitivity reactions.

2.1. Clinical association between HLAs and SCARs

Since 2001, several IADRs by small molecule drugs have been linked to different HLA alleles (Table 1). Abacavir is a nucleotide analog with antiviral activity against HIV-1. Approximately 5–7% of Caucasian patients develop hypersensitivity within 6 weeks of initial exposure to abacavir [15]. The strong association between the MHC class I allele HLA-B*57:01 and abacavir hypersensitivity was the first association identified and most well studied (odds ratio >900) [15–19]. Preprescription testing for HLA-B*57:01 reduced the frequency of hypersensitivity showing that genetic testing can have a powerful influence in reducing the burden associated with IADRs [20–22].

SCAR is considered to be a delayed-type IADR involving T-cells [23]. Recent reports have implicated the involvement of some HLA class I molecules in the development of drug-induced SCARs. Carbamazepine is widely used in the treatment of epilepsy, trigeminal neuralgia, and bipolar disorder. Carbamazepine- induced SJS/TEN has shown a strong (odds ratio >1000) association with HLA-B*15:02 in the Han Chinese population [24]. This association has also been replicated in several other Asian populations, including Thai [25,26], Malay [27] and Indian subjects [28] but not in white [29–31] and Japanese subjects [32,33]. Significant associations between HLA-B*15:11 and carbamazepine-induced SJS/TEN have been also found in Japanese patients (OR = 16.3) [34]. HLA-B*15:11 and HLA-B*15:02 belong to the same serotype, HLA-B75. The T-cell receptor (TCR) clonotype, Vβ-11-ISGSY is dominant for patients with carbamazepine SJS/TEN. Thus assumingly T-cell activation is not only restricted by HLA-B*15:02 but also TCR clonotypes [35]. Interestingly, CBZ-induced SCARs in Caucasian and Japanese populations is associated with HLA-A*31:01 [36,37]. HLA-B*15:02 and HLA-A*31:01 differ greatly in amino acid sequence, however they share two of the three residues suggested to control the interaction of CBZ and HLA-B*15:02 (95Ile and 156Leu but not 63Asn) [9]. It is important to note that this ethnic difference may relate to HLA-B*15:02 allele frequency and does not mean Caucasian/Japanese carriers of HLA-B*15:02 can be safely treated with carbamazepine.

Allopurinol is used as a urate-lowering drug and frequently causes SCARs [38]. All Han Chinese and Thai individuals with allopurinol-induced SCAR were found to express HLA-B*58:01. Furthermore, most Korean patients also expressed this allele [38–40]. In all of these populations, the frequency of the HLA-B*58:01 allele is high (6.5–10%) [39]. Nonetheless, 45% of patients of European ancestry with allopurinol induced SJS/TEN did not have HLA-B*58:01, suggesting that this allele is not an absolute risk factor [30]. Furthermore, the positive predictive value of HLA-B*58:01 is estimated to be only 2.7%, implying that other risk factors are also important [41]. Associations between other drug-induced SCARs and HLA alleles are summarized in Table 1 or reviewed in Refs. [4–6]. Interestingly so far, very strong association between MHC class II allele and SCARs has not been reported.

Table 1
Clinical association between HLAs and IADRs (from representative reports).

Drugs	Disease phenotype	HLA association	Odds ratio	Reference
Abacavir	Hypersensitivity	B*57:01	>900	[18,19]
Allopurinol	SJS/TEN/DRESS	B*58:01	50–580	[38,149]
Carbamazepine	SJS/TEN	B*15:02	>50–1000	[26,150,151]
		A*31:01	26/33	[36,37]
Clozapine	Agranulocytosis	DRB5*02:01	22	[53]
		B*38/DR*4	50/23.3	[55]
		B*59:01	10.7	[54]
Co-amoxicav (amoxicillin- clavulanate)	DILI	DRB1*15:01 and DQB1*06:02	2.8	[46–49]
		A*02:01	2.2	
Flucloxacillin	DILI	B*57:01	80.6	[42]
Lamotrigine	SJS/TEN	B*38	6.8	[30]
Lapatinib	DILI	DRB1*07:01, DQA1*02:01, DQB1*02:02	2–9	[50]
Levamisole	Agranulocytosis	B27		[56]
Lumiracoxib	DILI	DRB1*15:01	7.5	[51]
		DQB1*06:02	6.9	
		DRB5*01:01	7.2	
		DQA1*01:02	6.3	
Methazolamide	SJS/TEN	B*59:01	>250	[152,153]
Nevirapine	SCARs	B*35:05	19	[154]
Phenytoin	SJS/TEN	B*15:02	18.5	[25,155]
Ticlopidine	DILI	A*33:03	13	[44]
Ximelagatran	DILI	DRB1*07	4.4	[52]
		DQA1*02	4.4	

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