New approaches for predicting T cell–mediated drug reactions: A role for inducible and potentially preventable autoimmunity

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Adverse drug reactions (ADRs) are commonplace and occur when a drug binds to its intended pharmacologic target (type A ADR) or an unintended target (type B ADR). Immunologically mediated type B ADRs, such as drug hypersensitivity syndrome, drug reaction with eosinophilia and systemic symptoms syndrome, and Stevens-Johnson syndrome/toxic epidermal necrolysis, can be severe and result in a diverse set of clinical manifestations that include fever and rash, as well as multiple organ failure (liver, kidney, lungs, and/or heart) in the case of drug hypersensitivity syndrome. There is increasing evidence that specific HLA alleles influence the risk of drug reactions. Several features of T cell–mediated ADRs are strikingly similar to those displayed by patients with autoimmune diseases like type I diabetes, such as strong HLA association, organ-specific adaptive immune responses, viral involvement, and activation of innate immunity. There is a need to better predict patient populations at risk for immunologically mediated type B ADRs. Because methods to predict type 1 diabetes by using genetic and immunologic biomarkers have been developed to a high level of accuracy (predicting 100% of subjects likely to progress), new research strategies based on these methods might also improve the ability to predict drug hypersensitivity. (J Allergy Clin Immunol 2015;136:252-7.)

Key words: *T cell, adverse drug reaction, autoimmunity*

Abbreviations used
ADR: Adverse drug reaction
DILI: Drug-induced liver disease
DRESS: Drug reaction with eosinophilia and systemic symptoms
GAD: Glutamic acid decarboxylase
OR: Odds ratio
SJS: Stevens-Johnson syndrome
SLE: Systemic lupus erythematosus
TEN: Toxic epidermal necrolysis
Treg: Regulatory T

The intention of this review is to compare and contrast the features of T cell–mediated adverse drug reactions (ADRs) with those of autoimmunity as they relate to disease progression because understanding their similarities in pathogenesis will suggest future research strategies for establishing rationales to improve ADR case workups.

ADRs and autoimmunity differ in that ADRs have a relatively higher complexity of underlying immunologic responses (eg, drug reaction with eosinophilia and systemic symptoms [DRESS] syndrome, Stevens-Johnson syndrome [SJS]/toxic epidermal necrolysis [TEN], and erythema multiforme), which varies greatly among the different drugs, and the pathologies underlying autoimmune diseases are better understood than those of ADRs. In autoimmunity the understanding that adaptive immune responses are often established before disease onset has been taken advantage of in the clinic in terms of predicting disease progression. In a similar fashion, ADRs that stimulate T cell–mediated immune responses might benefit from new research investigating the rationale that using specific immunologic and genetic tests like those currently used to predict autoimmune diseases, including HLA typing, can also predict ADR occurrences.

SIMILARITIES: ADAPTIVE IMMUNE RESPONSES DIRECTED AGAINST SELF

Autoimmune diseases and drug hypersensitivity responses both involve stimulation of the adaptive immune system against self-proteins.[1-3] T cell–mediated ADRs involve anatomically directed adaptive immune responses, systemic responses, or both. For example, allopurinol and carbamazepine trigger SJS/TEN, in which cytotoxic $CD8^+$ T cells are thought to destroy keratinocytes at the dermal-epidermal junction by using the enzyme granulysin,[4] annexin,[5] and Fas ligand[6] as mechanisms for lysis. Amoxicillin clavulanate, flucloxacillin, and ximelagatran cause drug-induced liver disease (DILI) in certain subjects.[7] Abacavir is an example of a drug capable of triggering systemic T cell–mediated hypersensitivity responses in *HLA-B57:01*–positive at-risk patients[8]; these systemic symptoms can be lethal and include fever, rash, vomiting, abdominal pain, and multiple organ involvement.[9] Carbamazepine stimulates both anatomically directed T-cell responses and systemic responses.[10]

Many autoimmune disease pathologies also involve T-cell responses against self. In patients with rheumatoid arthritis, there are self-directed autoimmune responses against connective

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tissue components.[11] T-cell responses are directed against components of the dermis in patients with psoriasis.[12] In patients with celiac disease, exposure to gluten peptides initiates T cell–mediated autoimmune responses against transglutaminase-modified peptides expressed in self-tissues.[13,14] In patients with type 1 diabetes, T cell–mediated autoimmune responses are thought to destroy insulin-producing β cells in the pancreas.[15,16] Autoimmune responses and drug responses also frequently involve both T and B lymphocytes. In the setting of autoimmune diabetes, for example, patients can generate T-cell responses and autoantibodies directed against insulin, glutamic acid decarboxylase (GAD), islet antigen 2, and a zinc transporter.[17,18] Systemic lupus erythematosus (SLE), an autoimmune disease in which chronic inflammation is systemic, often affects the heart, joints, skin, lungs, blood vessels, liver, kidneys, and nervous system.[19,20]

Some drugs can even act as inducible triggers of autoimmunity in an HLA-associated manner. Hydralazine and isoniazid trigger drug-induced SLE in association with *HLA-DR4*.[21] D-penicillamine–induced myasthenia gravis associates with HLA-DR1.[22] Thiopurines associate with pancreatitis in patients with inflammatory bowel disease with the *HLA-DQA1*02:01/HLA-DRB1*07:01* haplotype, showing an odds ratio (OR) of 2.6.[23]

SIMILARITY: HLA ASSOCIATIONS

HLA associations have been found for nearly all autoimmune diseases.[2] The strength of association between HLA alleles and individual diseases varies significantly.[24] Some diseases, including asthma,[25] Crohn disease,[26] and ulcerative colitis,[27] show significant but weak HLA associations (OR, <2). HLA alleles are moderately associated (OR, 2-4) with SLE,[24] multiple sclerosis,[28] and autoimmune thyroid diseases, such as Graves disease and Hashimoto disease.[29] Ankylosing spondylitis,[30] celiac disease,[31] rheumatoid arthritis,[32] and type 1 diabetes[33] are strongly associated with HLA alleles (OR, >4). Differences in the strength of association between HLA alleles and individual diseases might reflect the variation in the role of T-cell responsiveness in the context of other environmental and genetic factors influencing the pathogenesis of a given disease.

HLA alleles are also associated with an increasing number of drug hypersensitivity responses. The strongest HLA-associated drug responses are between *HLA-B*57:01* and abacavir hypersensitivity syndrome in the white population, *HLA-B*15:02* and carbamazepine-induced SJS/TEN in Asian populations, and *HLA-B*58:01* in patients with allopurinol hypersensitivity syndrome and SJS/TEN (OR, >500).[34] Similar to autoimmune disorders, the strength of association between drug hypersensitivity and HLA alleles ranges from weak to strong. Significant associations between drug hypersensitivity and HLA alleles suggest their potential utility in predicting at-risk subjects. For abacavir, an HIV reverse transcriptase inhibitor, identification of the strong HLA association between abacavir hypersensitivity and *HLA-B*57:01* has led to a currently used prevention strategy[8] wherein a pharmacogenetic test is now routine in HIV clinical practice.[35]

Drugs are thought to elicit ADRs in an HLA-associated manner because they can interact with HLA molecules and form drug-HLA complexes capable of being recognized by T cells. Drugs can bind HLA in at least 3 possible ways. First, drugs can act as haptens, forming covalent interactions with peptides that bind HLA molecules associated with ADRs (eg, penicilloyl-modified peptides).[36] Second, drugs can bind directly to the T-cell receptor or HLA molecules outside of the antigen-binding cleft with rapid noncovalent interactions (called the pharmacologic interactions with immune receptors hypothesis).[37] Third, drugs can bind within the antigen-binding cleft of the HLA molecule, altering the repertoire of HLA-bound peptides; in this mechanism the drug enables the presentation of self (and possibly viral) T-cell epitopes to which the host is not tolerant.[38,39]

SIMILARITY: VIRAL INFECTION AND HETEROLOGOUS IMMUNITY

A number of drug hypersensitivity reactions and HLA allele associations occur in virally infected patients. The mechanistic roles of the viruses in the initiation or perpetuation of T cell–mediated ADRs are complex and have been proposed to involve stimulation of virus-specific T cells that cross-react with the drug presented to T cells in the context of HLA (the heterologous immunity model).

Evidence that viruses play a role in ADRs include ampicillin-induced exanthema in patients with mononucleosis (expressing activated EBV). Although exanthematous eruptions in patients with mononucleosis are relatively uncommon (rate, 10%), they are common among ampicillin-treated patients (100% of children and 70% of adults).[40] Similarly, the incidence of severe ADRs to co-trimoxazole is significantly lower in the general population compared with that in HIV-infected patients.[41]

Although viral infection likely influences T cell–mediated ADRs through a number of non–antigen-specific mechanisms (eg, by stimulating innate immunity), some specific viruses strongly correlate with adverse responses to certain drugs. For example, human herpesvirus 6 activation is associated with carbamazepine-induced DRESS syndrome, and reactivation is associated with slow recovery.[42] Also, HIV-infected patients with SJS exhibit viral reactivation (EBV and cytomegalovirus) on drug exposure.[43] The clinical effects of these virus-drug interactions range from mild (EBV-linked ampicillin rash) to severe (human herpesvirus 6 reactivation and DRESS syndrome).[44] Collectively, these observations demonstrate diversity in pathogenic mechanisms for ADRs.

Cytotoxic T lymphocytes specific for viral epitopes have been found to expand in patients with drug hypersensitivity reactions,[45] suggesting that the drug can stimulate T cells previously primed by viral exposure through a cross-reaction/molecular mimicry mechanism. The drug might also directly or indirectly stimulate viral reactivation and expression of viral proteins, thus resulting in increased presentation of viral epitopes and expansion of virus-specific T cells that promote ADRs.

Data suggest that pathogen infections influence autoimmunity. In patients with type 1 diabetes, there are strong antibody responses to coxsackievirus infections, and a similarity between the structure of the autoantigen GAD and the P2-C protein of Coxsackie B are implicated as a potential cross-reaction mechanism.[46] High titers of EBV-specific autoantibodies have been reported in both patients with multiple sclerosis[47] and those with SLE.[48] Rotavirus infections are strongly associated with celiac disease.[49] In addition to coxsackievirus infections, the intestinal microbiota can play a role in the development of autoimmune diabetes.[50] Thus the combination approach of defining environmental triggers (eg, viral

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